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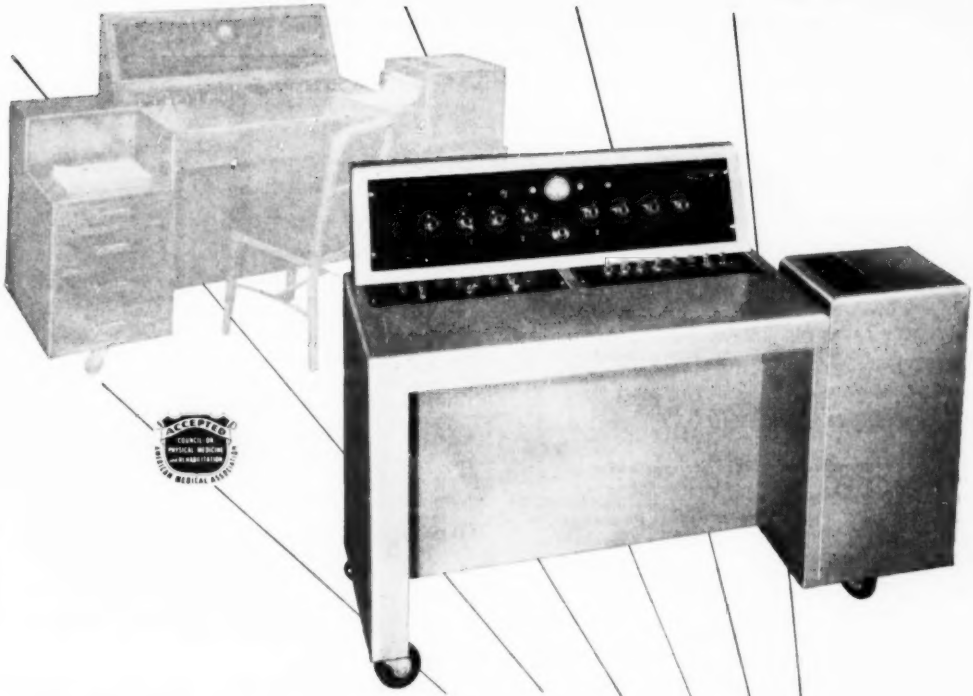

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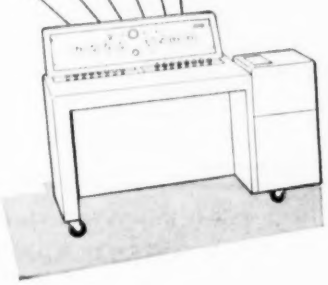

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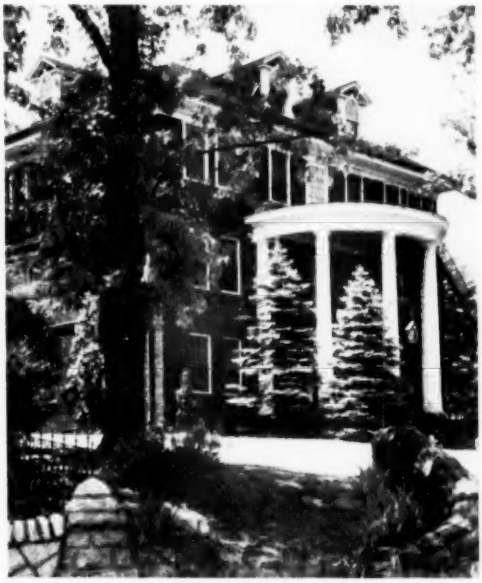

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VOLUME 70 SEPTEMBER 1953 NUMBER 3

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LANGUAGE AS EXPRESSIVE BEHAVIOR

MARIA LORENZ, M.D.
BOSTON

THE RELEVANCE of language study to psychiatry has received emphasis with respect both to the function of language as a process of symbolization and, more recently, to its role of communication. The theories of thought disturbance in psychopathological states are based upon the study of distortions of signification and meaning as reflected in language. Communication and information theory has its current impact upon psychiatric problems. These considerations of the major functions of language overshadow, perhaps, its aspect as a form of expressive behavior. The remarkable facility of language to mirror character and personality traits of the individual has a particular kind of value, which merits some discussion.

Language habits reflect the perception of experience and are a part of behavior from which inferences are drawn regarding the individual. It is probable that many such inferences, based upon an awareness and observation of language habits, are not made explicit but remain hidden in "intuitive" evaluations and judgments. These impressions can be differentiated and made more explicit by the recognition of their source. Moreover, language behavior is a medium readily at hand from which useful information pertaining to spontaneous psychological behavior rather than response to designed test situations can be abstracted.

The expressive functions of language as a carrier of cultural, social, and personality traits have been described by Sapir,[1] Newman,[2] Malinowski,[3] and others. Students of the psychology of language, notably Bühler,[4] Krechel,[5] and Dilthey,[6] suggest that, in addition to the peripheral aspects of personality, the broader categories of subjective experience, such as cognition, volition, and affect, can be traced in the pattern of language.

From the Psychiatric Service, Massachusetts General Hospital; the Massachusetts General Hospital Division of the Hall-Mercer Hospital, and the Department of Neurology and Psychiatry, Harvard Medical School.

1. Sapir, E.: Speech as a Personality Trait, Am. J. Sociol. **32**:892-905, 1927.

2. Newman, S. S.: Personal Symbolism in Language Patterns, Psychiatry **2**:177-184, 1937.

3. Malinowski, B.: The Problem of Meaning in Primitive Languages, in Ogden, C. K., and Richards, I. A.: The Meaning of Meaning, New York, Harcourt, Brace and Company, Inc., 1952.

4. Bühler, K.: Sprachtheorie, Jena, Germany, Gustav Fischer, 1934.

5. Krechel, J.: Persönlichkeitstypus und Sprache: Eine empirische Untersuchung über die Beziehung von Persönlichkeitstypus und Sprache, Arch. ges. Psychol. **89**:449-524, 1933.

6. Hodges, H.: The Philosophy of Wilhelm Dilthey, London, George Routledge & Kegan Paul, Ltd., 1952.

During the course of previous studies of language behavior in psychotic and psychoneurotic subjects [7] it was noted that very definite impressions emerged with respect to the general characterological make-up of the individual. The basis for these impressions lay only in part within the content of the communication. To an equal extent, they seemed to arise from considerations, difficult to particularize and formulate, but which can be designated under the term "expressive" function of language. A person automatically and unconsciously conveys his meaning in the form, relationships, organization, and habits of expression. These meanings are distinct from those derived from the factual content and from the physical attributes of speech. Here he reveals something of his basic attitudes, drives, and general orientation toward the self and the external world. Some general considerations and illustrations of this expressive nature of language behavior are presented here.

I. THEORETICAL ASPECTS

The complex nature of the psychological activities which are involved in a single act of language becomes apparent upon reflection. When a thought, feeling, or external event is formulated in language, the subjective experience as given is organized in a definite way.

To say "I see a boat on the river" is not to say "a boat is on the river" or "the river has a boat on it." Selection of one perception out of the entire field of perceptions has occurred. Attention is primarily pointed to the river, to the boat, or to the observer. The object selected is now fixed in consciousness for reflection and ready recall. The word symbol may have a specific referent and, at the same time, carry with it varying degrees of associative meaning. An assertion or judgment is made. The value of the statement may lie in disarticulating and analyzing a complex experience into its parts or in bringing together and synthesizing discrete elements into a whole. The situation is assigned a place in time; past, present, future; actual or hypothetical. The context may be presented as existing in reality or in imagination. Conscious and unconscious determinants effect what is said and how it is stated. Personal and social and cultural stylistic devices are used. Purpose, intent, and motivation color the expression.

These aspects of language, although not consciously taken into account, make their impact upon the listener. A simple demonstration will show that variables such as these, distinct from content, are involved in the appraisal of verbal communication. For the purpose of illustration, a sample of language falling within the range of the pathological is selected. It represents a segment of recorded interview material. A copy of this material, submitted to a group of psychiatrists, elicited a response, of which three representative statements are given given below:

"What do you want me to say? I was born Dec. 14, 1893. *Nicht wahr?* My father was almost 54 and my mother was 32. Let's see, she was born in '58. And I was an only child. I was a puny child. I talk too much, they tell me, but the doctor at the North Haven clinic said there were always things worth telling. I talked to him for two hours; of course, I was depressed. . . . He has dark hair and handsome eyes, you know, mongolian. . . . The

7. Lorenz, M. and Cobb, S.: Language Behavior in Manic Patients, A. M. A. Arch. Neurol. & Psychiat. **67**:763-770, 1952. Lorenz, M.: Language Behavior in Manic Patients: A Qualitative Study, ibid. **69**:14-26, 1953; Lorenz, M. and Cobb, S.: Language Behavior in Psychoneurotic Patients, ibid. **69**:684-694, 1953.

other one was one of those Steinmetz Jews. He said: *'Was haben wir hier?'* In German we say, *'Was ist los?'* Let's see, I was always *lustig*, manic personality, I guess. My mother died in May, after I graduated. I was married in 1915. My husband was a descendant of an English lord from the wrong side of the blanket."

Responses: Each of the three psychiatrists commented that this sample was the speech of a hypomanic patient. Each was asked upon what observation this judgment was based.

Psychiatrist A: Many themes. Variability of ideas. Essential intelligibility. Insight into knowing she is manic. Rather open hostility. Short sentences, each intelligible by itself. Superficial associations. Jocularity in last sentence. Sweep, fast rhythm to language.

Psychiatrist B: Distractible. Runs off on side lines. Throws in German sentences. Short, choppy arrangement. Superficial associations.

Psychiatrist C: Scattering. Wanders. No evidence of anxiety, doubt, confusion. Personal rumination. Flight of speech; flight of ideas. Accurate in calculations. Associations suggestive of mania. Calls herself depressed and manic. Gives facts most people would not discuss at all.

Observations are made with respect to both quality and quantity of content ("Many themes"; "variability of ideas"; "personal rumination"). The logic of relationships is noted ("essential intelligibility"; "each sentence intelligible in itself"; "flight of speech"; "flight of ideas"; "accuracy of calculations"). The quality of the associations is noted ("superficial"; "runs off on the side-lines"; "distractable"). Form, arrangement, and, by implication, grammar and syntax ("short"; "choppy"; "intelligible") are taken into account. In one instance the written language produced a distinct sensory impression ("sweep, fast rhythm"). The evocative function of language comes into play ("hostility," "open agression," and "jocularity" are attributed to the speaker). The incongruous (insertion of foreign phrases) and the unconventional (last sentence) strike the eye. The self-evaluation of the patient is considered of importance because she expresses it, as well as for its factual value.

A further, and important, point to note is the automatic response to language as a stimulus which, with very few consciously recognized explicit clues, calls forth mechanisms of projection, quick judgments and evaluation, and immediate emotional reactions and elicits recognition and recall of previous experiences with similar patterns of speech.

The inference that this is the language of a hypomanic patient appears to be based upon a complex set of psychological events that occur in both speaker and listener. On the one hand, language mirrors certain peculiarities and distortions of psychological processes occurring in the patient. On the other hand, it acts as a stimulus setting off a chain of associative psychological responses in the listener. It becomes apparent, then, that language acquires meaning only as part of a "triadic" situation,[8] whether real or hypothetical, involving speaker, hearer, and content.

II. OBSERVATIONS AND ILLUSTRATIONS

The second point raised in the introductory statements, namely, that useful clinical information can be extracted from attentive scrutiny of language, can be shown with quotations from transcribed interviews with psychoneurotic patients. The quotations are necessarily brief and are used as illustrations.

8. Urban, W. M.: Language and Reality, New York, The Macmillan Company, 1951.

Pattern.—A strong tendency to utilize characteristic habits of expression in the same and subsequent interviews was readily apparent. This can be confirmed by examination of transcribed interview material from any patient.

Examples of the characteristic pattern in which two patients with phobic preoccupations referred to their difficulties is given below.

L. M.: "*It just feels as if* I were fighting something that is unknown . . . and then at other times it is *just as if* I had the answer in my hand and it rolls out again, uh, it, it *seems as if* I *just* have to find an answer. There must be an answer. And the worst, the the more awful thought that I *seem* to think of, the lower my spirits sink *as if* they were going down in an elevator . . . I can't seem to get close to N . . . it's *just as if* someone had cut all the good parts out of me."

Analysis of complete interviews further showed that the "just as if" and "seem" mode was the patient's characteristic manner of formulating her complaints. In conjunction with this trend was a striking regularity in the use of words, such as "must," "must be," "has to be," "have to do," whenever the patient talked about expectations, the behavior of other people, or external events. It was further noted that "I" was most frequently linked with verbs of the "will" and "shall" category, and that "me" and "myself" loomed large in connection with passive verbs or what other people did to her—"Things just happen to me," or "He didn't make me feel better." The descriptive words occurring most frequently, although emotionally highly colored—"awful"; "frightful"—were conventional and trite. This patient did not dwell directly upon the ideational component of her obsessive thoughts. "Seems" and "as if" pointed strongly to the feelings and reaction aroused by them. One of her major difficulties lay in the "must" attitude toward external things that were outside her control.

By contrast, another patient (L. B.) expressed his phobic preoccupations in the following manner:

L. B.: "The thoughts of looking at a high building *used to bother* me, thoughts of being on a bridge, driving over a bridge *would bother* me. The thoughts of going underground in a subway or something *would bother* me, but that *doesn't bother* me, I think *I've conquered* that . . . but I still feel pretty miserable . . . well, I do know that at times when I'm feeling a little sensitive—it seems that when I'm sensitive is the time that I think of all the things I *shouldn't be* thinking of. . . . why do I *have to* think of those things. . . . I feel pretty miserable. . . . simple decisions that *should be* made and I make a problem of it, which I know I *shouldn't* make a problem of."

During many interviews this patient persistently described his symptoms as occurring in the actual past or the hypothetical past, never a clear-cut admission of "I am bothered by" or "I have thoughts," although he was currently suffering from these preoccupations. His insistence on having conquered them is contradicted by his admission of feeling miserable. This avoidance of an explicit admission of these thoughts, a set pattern for many months, was rooted in a conviction that talking about them made them real.

Further, one notes the frequent injunctions and prohibitions—"should be thinking," "decisions should be made," "I shouldn't make." The "should" note was struck again and again during interviews. Rigid superego demands and restrictions were involved in his neurotic conflicts.

In the speech of both these patients the stress was emphatically on the subjective feelings generated by these thoughts rather than on the content of the thoughts themselves.

In another patient, a loosely organized, vague, and rambling language behavior alternated with a terse, direct, quite specific structure and form. This paralleled, as indicated below, areas of self-appraisal, in which she was hesitant, tentative, and doubtful, and contrasted with areas of evaluating the subjective state of other people. Among this patient's problems was an attitude of low self-esteem, constantly joined to envious exaggeration of the capacities of others. During the course of therapeutic work it also developed that early parental patterns of aggressive self-assurance colored her appreciation of the subjective experience of others.

B. P. showed a change in pattern when talking of self or of other people:

B. P.: "I don't think there is any happiness really, except, or, I mean, there's nothing that you can do; it's just the way you think, I mean some people have a much greater capacity for happiness than others anyhow, I mean I just thought everybody knew that. I don't think I have a capacity as great a capacity as a great many people. I mean, some people, oh, I don't know, they have nothing, really (Yet you see S and B are happy. They have a wonderful time always, completely happy. B's so cheerful and jolly. Some people get things, get a lot of enjoyment out of everyday things. Some people go along in high spirits all the time. I know a girl and she doesn't know what it feels like to be depressed. She never feels poorly at all.) Well, of course, I mean, I've been told, uh, that I was very nervous and highstrung. I think there's a certain pattern I've been brought up to, uh, and, uh, really, I mean I've been brought up to, uh, and, uh, really, I mean, I'll never get rid of it, I mean, Oh, I don't know . . . but, uh, well, I don't know just how to explain it."

Emphasis on making assertions, appeal to the auditor, is apparent in D. W.'s language pattern to a degree that language has become a stereotyped and mechanical form of expression of a need to convince:

D. W.: "But I come home and I get more sickness on me, *you see what I mean.* It seems that I always get sick just the same, *you see what I mean.* I'm not saying I don't want to work; *don't get me wrong,* I know that I can't; *see what I mean?* I don't want anything to happen to her, *you know.* Maybe if she wasn't there, I would be able to get out and show myself, *you know what I mean,* but by knowing that my mother is there, I know that I can't, I know that she's there, *see what I mean?*"

In another patient, J. M., language pattern showed clearly the conditional attitude, linked with projection into the hypothetical future. This conveniently absolved him from assuming responsibility in the present. Sentences of the following grammatical pattern recurred constantly in every interview:

S. M.: "If I could . . . I would be . . ."
"If I did get . . . I would make . . ."
"There are lots of things I would like to . . . but . . ."
"If I kept up . . . I would come . . ."
"If I could learn . . . I probably wouldn't . . ."
"If I ever did . . . I suppose I would . . ."

In C. W. the elaborate use of connectives calls attention to a pseudological approach to experiences. "So," "therefore," "because," "since," "as a result of," "because of," "in consequence of" underscored all her discussions. Rationalization was one of her main defense mechanisms.

C. W.: "I couldn't say anything *because* I have found him quite intelligent in most conversations. *In fact,* I've taken girl friends down to talk to him. It breaks my heart to look

at him and to know there's nothing I can do. *So* I've been to see him seldom. Mother doesn't go often either. *Which* hurts me greatly. And *as a result* I have developed a sort of motherhood instinct in me. *Therefore* it hurts me psychologically, as well as physically, *because* I have what you might call false pregnancy. . . . he's always given me a feeling of usefulness *because* I've been able to comfort him. *So therefore*, that is my main objective in life.

In B. R. the constant use of negation—"I don't know why," "I can't see," "I don't feel," "I can't think," "It can't be," "I can't do"—and verbs denoting uncertainty—"I guess," "I think," "I try," "I suppose"—mirrored the abject and oppressive quality of self-evaluation, her helplessness, and insecurity.

B. R.: "*I don't know* why I associate a lot of things with myself. I try to pick out certain people, I *guess* the one's *I think* understand me, and *I don't know*, sometimes I *question* afterwards, are they really interested? *I can't have* the feeling, *I don't know*, that they understand."

The quality of the modifying terms used points to quite different attitudes and evaluations of experience. E. C. qualified in terms of quantity and degree:

E. C.: "I *always* feel that he had been *very* close to me. It is a *very* morbid sense, I have a *very* morbid sense of going into the house alone; I *just* hate walking in; I *just* shrink with fear; I guess I'm *more* angry with myself than *anything* else; I know I felt *very* irritable. I felt *very, very* bad about that."

Taking one page of recorded interview material, one noted a preponderance of the following expressions: a *lot* of people; *all* the way; *one* person; *any* joy; *one* thing; *many* people; *all* over her; the *only* time; *quite* a bit; *number* of people; a *few;* a *lot* of other things; the *whole* scene; has *always* spoken; *anything, everything.*

By contrast, a quite different mode of perception is noted in M. H.:

M. H.: "I felt *terribly* wicked; I suffered *terribly, terribly* because it seemed so *awful.* I was *horrified.* I get such *guilty* feelings; I feel *terribly* guilty, a *terribly* feeling, the most *horrible* thing; what more *horrible* thing could I do?"

Her choice of adjectives and descriptive phrases lined up as follows: a *wonderful* feeling; *pretty, nice* feeling; *dark horrible* feeling; *terrible* feeling; *foolish* feeling; I think it's *foolish;* I think it's really *nice;* I have these *dark, awful* thought; I was simply *fascinated;* I felt *sad,* but sort of a *pleasant* way.

Each of these patterns was habitual and recurrent in the patient's mode of expression irrespective of topic and content. The psychological meaning of this language habit is relevant only in conjunction with other traits that appear in the language pattern. Descriptively, one can point to the exaggerated effect of subjective coloring of the M. H. pattern, and yet its limitation to socially acceptable words of description, and to the more objective, quantifying, and limiting pattern of E. C., with its suggestion of an attitude which measures everything.

L. H. could speak of herself only in terms of the following kind of sentences:

L. H.: "I *should* be able to hold my head up to go any place."
"I figure a girl *should* be a little more poised."
"I suppose I *should* become more conscious of the fact."
"It's not *necessary to feel that way.*"
"I *should* have kept on."
"We *should* have been closer."
"I mean I *shouldn't* be remembering it."

This patient lived with an idealized self-image and could express only expectations of herself, with very little recognition or acceptance of her actual self.

The constant use of emphasis, negation, and denial in H. B. suggests a need to convince and anticipation that her complaints will be doubted.

H. B.: " . . . I don't know which is worse, my face or my legs. They hurt me terrible. *Really,* Dr. B., with all my heart they're *really* painful. I'm *not* making believe; they *really* are. And I'm *so* unhappy because they treat it so lightly. They . . . they . . . I don't know, there hasn't been a thing done for me. I've had to do . . . now I haven't had a bath for weeks and nobody even cares. I just . . . I can't do it . . . because they hurt, and, err, so . . . I mean, I know it's a psychiatric ward, but isn't there a little bit of medical attention? I mean . . . I'm *not* making believe, *really* I'm *not.*"

"And I *don't want* to be . . . to be . . . be treated as though I'm pampered, I . . . I *don't want* to be pampered.. *Believe me.* I *mean* I *never* had a chance to be pampered all my life. I did all the pampering, and that's the *last thing* I'd want . . . to be pampered."

Object Relationship and Self-Evaluation.—A great variety of patterns with regard to object relationship manifest themselves in patients. When these patterns stand out strongly, they point to character traits and attitudes that require analysis, as well as the more explicitly formulated dynamics. One patient speaks consistently of herself in terms of certainty and directness—"I do"; "I think"; "I know," etc.—but becomes unconsciously tentative and doubtful in projecting feelings or emotions to others—her habitual organization of her observation of other people was always "he might be," "maybe," "it suggests that she feel," "it seems like he . . ." Another patient approaches the objective world in the speculative setting of "I wonder if," "could it be"—remote, detached, interested, rather than involved. Still another encompasses and confuses his own reactions with those projected into other people—all observations are made in generalities employing "you" as a common denominator.

The habitual pattern of reference toward the "I," the relationship between the personal pronoun and the predicate, as revealed in the voice, mood, and tense of verb, is often revealing. It is sometimes strongly suggestive of an egocentric point of view predominantly active or passive, locked in the past or projected into the future. One person may habitually describe his experiences by "I am troubled by," "I am disturbed by," "it hurt me," etc., whereas another states the same feeling with "I dislike," "I object to," "I hate it," etc. In the first instance a more passive, experiencing attitude is suggested than in the second. The quality of verbs used in referring to the "I" is often remarkably consistent. One patient may rely chiefly on verbs of a thinking, evaluating, judging order ("I suppose," "I think," "it appears," "or it seems to be," etc.); another uses feeling-toned and emotionally colored verbs ("I like," "I hate," "I love," "I feel," etc.); a third may remain fixed to "ought," "should," etc. Sometimes these characteristic forms of expression are reinforced by others to give a strong indication of predominant ego or id function or the inhibitions and demands of a strict superego. The patients who describe subjective experiences predominantly in terms of feeling or in terms of wishing and yearning ("I would like," "I want," "I wish," etc.) or in terms of "will" and "shall" present different therapeutic problems, however similar the object of their striving. Words denoting certainty, purposiveness, negation, or doubt sometimes run like a strong thread through an interview. "I certainly have," "I believe I can," "I am sure," "I don't," "never," "always," appearing frequently, give a different

flavor than "it seems as if," "may be," "perhaps," "possibly." The person who prefaces every other statement with "I think" probably holds his opinions with less certainty and confidence than the speaker who states his views directly.

Organization, Effectiveness, and Function.—The preferred pattern in which a patient expresses his comments and observations about people or events is often revealing. Where one patient tends to be descriptive and anecdotal, another scarcely touches upon facts but presents his value judgments; another, his emotional reactions. One patient will focus upon an accurate or vivid representation; another gives an idealized account. Ability to organize, to marshal facts and observations into effective sequence can be discerned readily in the language pattern. They may vary sensitively as the patient approaches areas that are emotionally charged or only dimly perceived.

The ability of the patient to communicate his thoughts is governed by multiple factors. Some of these are temporary, such as incentive, need, emotional attitude, and sanctions determined by the situation and the listener. There also appears to be a variation in the specific aptitude for translating inner experiences into language. With some persons language seems to serve as a transparent medium which transmits the uniqueness of personal experiences. With others language obscures more than it reveals. Such a screen may be erected by a rigid, conventional, class-conscious code. The use of language as an "intellectualizing" defense mechanism is another example. Where one patient uses language to achieve distance from his problem and to provide material for mutual inspection, another patient uses language specifically to build the impression he is trying to create or to gain the ends he has in mind.

Inability to communicate effectively in language, within certain areas and at certain times, is common to most persons. Blocking and inhibition and the opposite extremes, pressure of speech and logorrhea, are pathological deviations promptly recognized. Subtler variations are arrest in flow and direction of ideas, the appearance of monotony and repetitiousness, and paraphrasing, rather than the development of ideas and observations. Under stress of anxiety and strong emotions, the qualifying and differentiating parts of speech are apt to be decreased; sentence structure becomes less logical and coherent. Sometimes pronounced changes in the pattern of language occur as the focus shifts from using language primarily as communication to "thinking out loud." The degree by which the individual's pattern exposes or conceals may alter from explicitness, exhaustiveness, and elaboration to proceeding by hints, innuendos, and obscurities.

The functions of language are multiple, but often, in a given patient or in a specific interview, one or another of its functions is in dominance. It is not difficult to recognize when language is used primarily for catharsis, to discharge emotions, to ease anxiety. Its use as an instrument to control the immediate environment, by propagandizing, persuasion, coercion, an appeal to logic; to secure empathy, understanding, or to bridge isolation, is also often quite clearly apparent. Less obvious, but psychologically revealing, are the uses of language that arise from their unconscious meaning for the patient rather than in connection with their apparent effect. It may be used as a substitute for action, a form of exhibitionism, or for the securing of narcissistic gratification.

COMMENT

Illustrations are presented to support the view that the "how" as well as the "what" of communication effects the interpretation and understanding of language behavior. Form and structure in language, as well as content, have psychological meaning. When one observes attentively the language pattern of individuals, details stand out in sharp relief. The arrangement of grammatical categories to achieve ordered communication, the habitual use of words and phrases, the choice of vocabulary, all blend to create a pattern as distinct for the individual as his personal signature. From this pattern, inferences can be drawn with respect to object relationship, self-awareness, and general psychological orientation of the person. Habits of thought, mental set, and emotional attitudes, taken together with the immediate content of an experience, are factors which determine the meaning of the total experience for the individual. These component elements can to a degree be discerned in language, which is part of his general pattern of expressive behavior.

SUMMARY

In this paper examples are shown in which the speaker gave indirect evidence of certain of his personal characteristics. The points used in the approach to the study of the expressive function of language are briefly summarized.

Pattern.—A general pattern or style, in which focus and emphasis are placed upon one or several recurrent characteristics, is consistent for each individual.

Categories of Grammar and Syntax.—The selection of categories of grammar and syntax, although determined in part by content, is also dictated by the orientation of the speaker and reflects something of the meaning that the content holds for him.

From these observations the following inferences are drawn:

(*a*) Object relationship is often mirrored in the choice of predicate, whether predominantly cognitive, affective, or volitional, and in the qualifying attributes or speech.

(*b*) Attitudes of self-awareness, if primarily receptive or aggressive, may appear in the predominant use of active or passive voice and in the use of words of negation, doubt, and emphasis.

(*c*) Responsiveness to the environment may be noted in the type of qualifying adjectives and adverbs. The meticulous, pedantic attitude may be reflected in a consistent use of limiting and modifying words or phrases. Imaginative play of emotional and subjective coloring, or the trite and conventional, may be mirrored in the choice of substantives and adjectives.

(*d*) Subjective orientation in time, whether predominantly past, present, or future, actual or hypothetical, appears in the tense of verbs.

(*e*) Defense mechanisms, such as denial and overcompensation, may be in the foreground, as shown by consistent use of superlatives, words of emphasis, and expressions of negation.

(*f*) The immediate purpose, motivation, and effectiveness of langauge are important considerations.

These features of language are suggestive illustrations and require confirmation and expansion.

DYNAMICS OF THE CURE IN PSYCHIATRY

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AT THE very basis of the science of the healing art lies the problem of how the physician effects a cure. Since the most ancient of times the very best among physicians have been impelled to venture some judgment on this score.

The Greeks, the Romans, and their heritors held that it was only nature that heals. The physician merely treats—*Natura sanat: medicus curat.* This dictum was tersely paraphrased by Ambroise Paré—"Je le pansay, Dieu le guarit" ("I bandaged him, but God cured him"). This affirmation of the physician's limited function is likewise reflected in the terms "therapist" and "therapeutics"; these words are derived from the Greek term *θεράπων*, which means "servant." The physician's modest pretensions, wherein the greater credit for the cure is given to nature or, in later times, to God, may indeed have stemmed from his inherent humility. Some skeptics, however, have suggested that they served him rather as a shield against blame. For if the issue of a case rests with nature, or with God, then, should the treatment fail or the patient die, the physician can disclaim responsibility. Palpably, it must have been God's wish or nature's intention, and not the physician's fault.

But whatever might have motivated the physician's modest pretensions, fulfilling his obligations as a scientist, he at all times held to some theory on the causation of disease and had some concept of the dynamics of the cure.

The two were ever intertwined, and medical history clearly shows that the concepts of the dynamics of the cure were consistently related to the prevailing theories on the causation of disease, so that in any given period the prevailing theory on the dynamics of the cure mirrored the prevailing theory on etiology. Treatment and etiology can be taken as the two interrelated components which together summate the prevailing science of medicine.

How the dynamics of the cure related to the theory of the cause of disease is reflected in the following historical data.

When the physician conceived of disease as resulting from an imbalance in the humors of the body, that is, from a dyscrasia, he sought to effect a cure by reestablishing harmony in the humors. This he undertook to achieve by means of diets, purges, emetics, sweats, and the like. When the physician ascribed disease to evil spirits, he practiced exorcism. When the physician became an iatrochemist, he administered crude chemical elements, aiming at the reestablishment of the chemical harmony of the body, which he assumed had been disturbed in the disease process.

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In the 18th century, when the etiology of disease was conceptualized in terms of "sthenic" and "asthenic" states, the two cardinal remedies were antispasmodics and stimulants—opium and alcohol.[1]

When, in the 19th century, histology came to the fore, and Virchow developed the science of cellular pathology, the theory of humoral pathology was rejected, and with it also much of the therapeutic practice based theron.

Later still, when cellular pathology was, in turn, overshadowed by the great achievements of Pasteur and Koch, the etiology of disease was conceptualized almost entirely in terms of micro-organisms, and therapy, in terms of vaccines, antitoxins, and immune sera.

Psychiatry, which for many centuries was an integrated part of the science and the practice of medicine, shared in the prevailing theories, both as to etiology and as to dynamics of the cure. This is neatly reflected in certain terms still common in psychiatric vernacular—terms which by the evidence of their derivation illuminate also the "systems" of medical thought wherein they were coined. Thus, melancholia, phrenitis, mania, hysteria, and splenitis not only designate certain morbid conditions but point also to certain specific theories on the causation of psychiatric and other disorders. But psychiatry, as a distinctive medical specialty, did not come into being until comparatively recent times. It is not therefore germane to our purpose to dwell on the dynamics of the psychiatric cure as conceived of in ancient times. We need, rather, to confine our studies to the past 150 years. Yet I must make it clear that by this circumscription I do not intend to disparage the antecedent generations of medical men or to deny that among them there were many excellent psychiatrists and psychotherapists. I am not one of those who holds that psychiatry is the creation of modern science. On the contrary, I am quite certain that historically the "psychotherapist" antedated the "clinician." It is not psychiatry as such but only the specialty of psychiatry that is of modern origin. Hence if one desires to study the singular dynamics of the psychiatric cure, one is obliged to limit oneself to the time during which the etiology of mental and emotional disorders, and the rationale of their treatment, became and remained the predominant concern of a group of men who ventured definitive theories thereon. There is some arbitrariness in this time limitation, but it derives not from me but from the historic reality.

Medical history, I have said, teaches us that "the dynamics of the cure is mirrored in the prevailing theory on etiology." Reviewing the past 150 years, we find that the theories on the etiology of psychiatric illnesses, which held and still hold sway, can be listed under eight descriptive headings: (1) the daemoniacal-moral, (2) the hereditary-constitutional, (3) the toxic-traumatic, (4) the asthenic-disintegrative, (5) the repressive-analytical, (6) the ergological, (7) the socio-environmental, and (8) the ecological.

I have listed these theories in their approximate historical sequence, the oldest first and the newest last; but it must be recognized that the neatness, both of their designation and of their order is, in a measure, an artifact of systematization.

There may be some difficulty in recognizing the first division, that is, the daemoniacal and moral, as among the prevailing theories on the etiology of psychiatric disorders. This is, in part, due to the fact that some medical historians have

1. Brown, John: Elementa medicinae, Edinburgh, C. Elliot, 1780.

overemphasized Christian demonology and witch hunting. The daemoniacal-moral theory is to be understood in terms not of the Christian devil, but of the daemon of Socrates, and as it is today propounded by Carl Jung and by Maeder. I shall treat this much misunderstood and much underrated etiological theory later.

In contemplating the remaining seven etiological theories, one cannot but recognize that the scope for therapeutic effort which they singly allow differs very greatly. Thus, the psychotherapist can palpably do but little to countereffect malignant constitutional and hereditary factors, and that little is not psychotherapeutic in character. As much must be said of the psychotherapist's function in relation to the toxic-traumatic factors. At best, his task is to diagnose differentially the psychopathology due to toxic and traumatic causes and that due to other causes. Detoxication and the repair, where possible, of trauma do not generally lie within the psychotherapist's competence and obligations.

The therapy practiced by those who subscribed to the asthenic-disintegrative theory is largely in the nature of seclusion, rest, reeducation, and the softening and lightening of the trials and burdens of life. Here, though the psychotherapist's role is somewhat more active, it is still a minor one in the total operation.

Summating, then, the three categories, the hereditary-constitutional, the toxic-traumatic, and the asthenic-disintegrative, we see that in effect they afford relatively little scope for immediate psychotherapy. Within their logical framework, the dynamics of the cure operate far less in and through the person and skills of the psychotherapist than in and through the physical and environmental agents which he may employ, or which, as is more commonly the case, are employed by others under his remote supervision and according to his instructions.

At this point I want to comment on certain seeming incongruities in my recitation. I have listed eight etiological theories in the presumed order of their historical sequence. But they do not form a "chain" of theories. The later one does not necessarily link to, or displace, the earlier one. It may modify the significance of antecedent theories and constrict their applicability. But in actuality the eight listed etiological theories are currently coexistent and to some extent complementary. They form the synthetical body of etiological lore. Historically, however, these theories were each advanced, if not as the solely valid, certainly as the dominant and the superior, theory on the etiology of psychiatric disorders.

I underscore this because this historical actuality enables us to divide the history of modern psychiatry into two distinct periods: the period antecedent to, and the period following on, the introduction of psychoanalysis by Freud. The first period, extending from the late 18th until the beginning of the 20th century, can be designated as the organic, physiological, and descriptive era. The period following is best labeled as the era of dynamic psychiatry.

Before turning to the time since Freud, it will profit us to observe more closely the stage setting of his advent. Between 1800 and 1900 the structure and the operations of the nervous system were intensively studied. Interest in the immediate problem of the etiology of mental illness and in the dynamics of the psychiatric cure waned. It was expected that such problems would be dissipated by the very revelations certain to issue from the anatomicophysiological studies then so feverishly cultivated. Many, and among them Theodore Meynert, Freud's teacher, denied that psychiatry, as distinct from neurophysiology, could ever become a

legitimate specialty. Mental and emotional disorders, they held, were the result of physiological and organic disturbances in the nervous system and hence belonged in the field of neurology.

There was still another reason that psychiatry was in a state of "suspended animation" during the second half of the 19th century—it was, in effect, fixated by a great expectation. The period was surcharged with great hopes. Many earnest scientists entertained the most extravagant ideas on what medicine was likely to discover "on the morrow." Psychiatry, too, was awaiting the dawn of a new era. It was anticipating some great issue—something like the discovery of the "germ of insanity" or a specific serum or antitoxin against the neuroses and the psychoses.

Toward the very end of the 19th century a "something" did come forth. But it did not conform to what had been anticipated, and it was not welcome. That something was Freud's psychoanalysis. Freud's theories cut across the assurances, and disturbed the complacencies, of his contemporary world. Psychoanalytic theory was most disturbing precisely because it was not mechanistically oriented. Freud did not challenge the validity of what was known of neural structure and neurophysiology. He had been a neurologist before he turned to psychiatry. Freud, however, denied that the totality of human behavior could be accounted for on the basis of neuroanatomy and neurophysiology. Furthermore, he challenged the usefulness and denied the ultimate effectiveness of the then common modalities of psychotherapy—of hypnotism, suggestion, persuasion, reeducation, and electrostimulation.

Freud advanced an entirely new theory on the etiology of the psychoneurosis, that of repression. And for the treatment of the pathology resulting from repression, he developed a fundamentally new and novel technique, that of free association. Both these theories were in time greatly elaborated by Freud himself and by his disciples. They, however, remain the foundation basis of psychoanalysis. "It is possible," wrote Freud,[2] "to take repression as a center and to bring all elements of psychoanalytic theory into relation with it." Zilboorg,[3] also affirms: "Unless the method of free association is carried through, the process of a new affective reintegration of the personality as a whole cannot achieve its therapeutic or scientific goal."

Because psychoanalytic theory has permeated so much of current psychiatric thought and practice, it is desirable to examine closely the theory of psychoanalytic etiology and the dynamics of psychoanalytic cure. To particularize the processes of repression, one may note that Freud postulated the existence of the id, which embraces the primal urges: the superego, which is the socially oriented, inhibiting, conscience-including component of the psychic organism, and the ego, which is, in effect, that part of the psyche immediately in contact with reality, and which impinges upon, and is impinged upon derivatively by, both the id and the superego.

This tripartite division of the psychic mechanism was not original with Freud. It is an ancient trinity found almost universally in philosophy, psychology, and religion. What is original with Freud is his theory on the conflict between the id impulsion and the superego, resulting in the repression of unacceptable impulsions.

2. Freud, S.: An Autobiographical Study, Ed. 2., authorized translation, by J. Strachey, London, Hogarth Press, 1952.

3. Zilboorg, G.: Some Sidelights on Free Associations, Internat. J. Psycho-Analysis **33**:488, 1952.

Two factors in this formulation must be noted carefully, namely, that the repression is an unconscious act—it does not reach awareness—and that the repressed impulsion is not annihilated but may become operative and influence emotion, mentation, and behavior in vicarious, and not understandable, ways. The emergence and operation of the repressed are reflected in the psychopathology of everyday life, in dreams, and in the neuroses.

Because unconscious material, according to Freud, cannot be reached by any deliberate effort in recall but will well up in uncensored thought, free association, again according to Freud, is the essential and all-powerful therapeutic instrumentality of psychoanalytic psychotherapy.

To round out this exposition of the dynamics of the psychoanalytic cure, it is necessary to note that unconscious repressed material when brought into awareness is, according to psychoanalytic theory, deprived of its psychopathogenic energy and the integrated and integrative powers of the ego are thereby increased and improved. Lest I be later challenged on the last point, let me add now that I am cognizant of the fact that mere recall of repressed material is acknowledged by some analysts to be insufficient for "a cure." But this acknowledgment is a late acquired insight and, as a matter of fact, constitutes not an amplification of the original theory, but, rather, a challenge which is in effect tantamount to a contradiction of it. I shall deal with this issue later.

Freud's theory of repression and his theory of recall by free association are both brilliantly conceived. Furthermore, experience shows that the formulations of psychoanalytic theory are valid in many instances. Certainly, as already observed, the theory of repression is supported in much of the psychopathology of everyday life, in the dream process, as revealed through dream analysis, in a good deal of hysteria, and in the obsessive and compulsive neuroses. But, when all this is granted, pertinent and troubling questions remain to be resolved. Accepting, as one must, the reality of repression, one is yet obliged to differentiate between repression as a psychic mechanism and repression as a psychopathogenic process. That repression is as frequently and as dominantly psychopathogenic as Freud maintains is open to question. The analysts themselves recognize this, professing that "during the last twenty years or so it has become obvious that the mere uncovering of the unconscious is not enough. Not even full recollection of the forgotten events of one's life and the liberation from their repressed state of the various unconscious representations as well as affects, is enough." [3]

Repression may be, and in some instances is, the most prominent and the most powerful psychopathogenic factor. Repression is to some degree present in and contributory to every case of neurosis. But there are other psychological factors which to the unprejudiced student appear to be as powerfully pathogenic as, and more widely operative than, repression. Among these, deprivation is the most significant. By deprivation I intend the lack of some experience, or function, essential to healthy normal maturation. The orphan, the child of a broken family, the unloved child, the overindulged and pampered child, the child of immature and inadequate parents, the child born into times and circumstances of social turmoil and instability—such children are likely to suffer deprivations in physical, social, and psychic experience, deprivations which in the extreme will cripple them irreparably, and which in the more modest degrees may result in asocial, inadequate, and neurotic function and behavior. In such instances the dynamics of the cure

cannot lie in "free association" but must depend, rather, on substitutive and corrective experience, and in this the psychotherapist can play an important and determining role. Since a great number of crippling deprivations derive from untoward interpersonal relations which the patient experienced, mainly during childhood—relations to parents, siblings, other family members, nurses, and teachers—the countertransference of the therapist, to use this rather apt analytic term, provides an opportunity and a means for healing. "The therapist," as Franz Alexander has phrased it in another connection,[4] "must assume an attitude towards the patient which in the light of the patient's history appears appropriate to undo the pathogenic influences." I would add, "not only to undo but also to amend," for the cure is not always and ever a matter of "taking away." Oftener it is a task of "adding a something that was missed."

Only a few among the so-called orthodox analysts have recognized the pathogenic import of deprivation. That concept, however, was implicit in the ergological theories of Meyerian psychiatry.

To pursue further the dynamics of the cure in psychoanalysis, we need to examine closer the τέχνη of free association. Zilboorg, in his recent paper,[5] freely grants that the true psychology of psychoanalysis remains unknown and will remain so until the processes involved in free associations are fully understood. These processes, he affirms, are little known. Despite that, he describes free associations "as requiring a deliberate weakening, or attenuation, of that conscious part of the ego which deals with the outside world in order to permit the unconscious trends to slide, as it were, into the preconscious and from there to come to the surface and slip into the conscious."[5] This is neatly phrased, but it does not meet the challenge of the crucial question: In free association, what is the Censor that censors the Censor? The obvious fact is that free associations are never free. Free associations are subject to the same laws of psychological determination as those that govern all thinking.

It is patent that the therapeutic function of free association is greatly overassessed and much misconceived in psychoanalysis. For one thing, all recall, whether "directed or free," is unconscious, and such benefits as are derived from what is termed free association stem largely from the permissive atmosphere which embraces both the patient and the therapist, rather than from any presumed attenuation or deliberate weakening of any portion of the ego or the superego.

We can concur with Zilboorg's statement that "psychoanalysts know little of the process and the laws of free association." However, this is not tantamount to saying that little *is* known about free association. The ignorance appears, rather, to be confined to the psychoanalysts. Experimental psychologists, for example, know a great deal about free association. They have long been concerned with the dynamics of free association, and historically, be it noted, there was a school of analytical psychology[6] before there was one of analytical psychiatry. Furthermore, one of the original and principal propositions in analytical psychology is embodied in psychoanalytic theory. That is the postulate that all "mental life is directed,

4. Alexander, F.: Congrès international de psychiatrie, Vol. 5: Psychotherapie psychoanalyse, médecine psychosomatique. Evolution et tendances actuelles de la psychoanalyse, Paris, Librairie scientifique Hermann & Cie, 1950.

5. Hartmann, H.: Grundlagen der Psychoanalyse, Leipzig, Georg Thieme, 1927.

6. Stout, G. F.: Analytic Psychology, London, S. Sonneschein & Co., 1902.

purposive, motivated, and cannot be explained as being governed by the chance clashing of elements derived haphazardly from without."[7] Freud, similarly, advanced the postulate that both thought and action are determined by wish and motive. Heinz Hartmann would have us believe that Freud anticipated these findings of the analytical psychologists,[8] but R. Adamson wrote in 1884 that "thinking is motivated," and F. A. Bradley stated in 1887 that "thinking is controlled by the object of thought."[9]

The "operation of thought," which embraces free association, has been studied since the time of Aristotle, and most intensively during the past 100 years. The idea that all thinking is motivated, directed, and motored, that it is therefore not free, is almost universally accepted by all schools of psychology. The sole exceptions are the Pavlovians and the behaviorists, who espouse a modern version of the ancient associational theory. But here we need to emphasize that all thinking, not merely that reflected in so-called free association, is motivated and directed. The distorting emphasis on "free association" found in psychoanalytic doxy would make it appear that only in the "material" produced by free association can one find clues to the patient's conflicts and repressions. This is most certainly not the case. Freud himself, it will be recalled, observed that in the case of Mrs. Emmy he was struck by the lack in her formal recitation of any references to her sexual life and experiences:

> I was also struck by the fact that of all the intimate information imparted by the patient, the sexual element . . . was entirely lacking. . . . What she allowed me to hear was probably an *editio in usum Delphini* of her life's history.[10]

Freud did not need to elicit her "free associations" to ascertain the existence of this blind spot. It proved as obtrusive in her deliberate story as it would have been patent in her dreams.

It is not my intention to deny that "free association" is likely to be more productive of significant anamnestic and "forgotten" material than is orderly, deliberate recitation. I would, however, deny that "free association" is a unique process of mentation, involving, as it is postulated, an attentuation, and deliberate weakening of any part of the conscious ego. What is termed free association is in essence no more than the basic processes of thinking and recall, exercised in an extraordinarily permissive atmosphere. The psychotherapeutic situation and relationship facilitate what the world at large denies—a broad, inclusive, leisurely, judgment-withholding, sympathetic scrutiny of past experiences, present problems, possible alternatives, and much more beside.

Rado has also come to appreciate the cardinal significance of the permissive factor in the therapeutic relationship. Discussing Breuer's patient and the release she experienced when she vented her anger, Rado[11] observes:

> Another crucial point is that the patient *felt free* to recall the incident responsible for her rage. Had she feared that Breuer might criticize her, she would have remained silent or vented her anger on Breuer.

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7. Humphrey, G.: Thinking—An Introduction to Its Psychology, London, Methuen & Co. Ltd., 1951, p. 9.

8. Hartmann,[5] p. 65.

9. Cited by Humphrey,[7] p. 26.

10. Breuer, J., and Freud, S.: Studies in Hysteria, authorized translation by A. A. Brill, in Nervous and Mental Diseases Monograph Series No. 61, 1936, p. 74.

11. Rado, S.: Recent Advances of Psychoanalytic Therapy, A. Res. Nerv. & Ment. Dis., Proc. **31**:42, 1953.

I have belabored the subject of free association because, although it is badly understood, it has become a shibboleth in psychoanalysis. As such, it not only impedes progress in psychoanalysis but also is responsible for much drag and lag in therapy, the waste of much good money, and the loss of precious time. There is something of magical expectancy in the orthodox evaluation of free association—the expectation that if the patient recumbent will but free-associate long enough all things, including the good life, will ultimately come to him. This, like all magical expectation, constitutes nonsense.

On the other hand, for the achievement of good therapeutic results, it is essential that the psychiatrist, and even more so the patient, should acquire a thoroughgoing, all-embracing knowledge and understanding of the patient's experiences, reactions, rationalizations, and attitudes. For this the patient must have the opportunity for and the circumstances conducive to full and uninhibited recall and recitation. The permissive relationship of the therapist is here the essential prerequisite. But this relationship does not necessarily involve the patient in interminable, meandering verbigerations, nor does it preclude the offering of directions and suggestions by the therapist. On the contrary, if the therapist will draw his clues from the "motivations" patent in the overt behavior and in the formal recitations of the patient, he will find in them profitable guidance to the anamnestic terrains to be explored. He and the patient will thus the sooner acquire a clear understanding of the significant components of the patient's total experience. Therapeutic expeditiousness and therapeutic effectiveness will thus be favored.

All this obviously presupposes much more active participation in the "therapeutic process" than is countenanced in orthodox psychoanalysis. On this score it were easy to opine—"so much the worse for orthodoxy." But that would do no justice to the historical validity entombed in the objection. Then, besides the orthodox analysts, we need to bear in mind some among the clinical psychologists, and some among the social workers, to whom the concept of nondirective therapy is so very precious, and to whom the opposite carries so much of anathema.

As far as Freud and his early associates are concerned, we need to recall that they were inordinately sensitive to "therapeutic activity," for to them it meant a kind of "moralistic busybodyness," with which they were all too painfully well acquainted. Griesinger had no sympathy with "the moralising ideas that were held by bigots regarding the treatment of insanity."[12] Yet under the heading of the more direct moral action for the purpose of restoring mental health, he advised that morbid ideas which repress and conceal the former (healthy) individuality must "be uprooted and destroyed, while the old ego must as far as possible be recalled and strengthened."[13]

This is a far cry from the therapeutic activity which seeks to guide the patient in the exploration of certain segments of his history wherein he might find insight into the derivations of his past and current difficulties. As far as nondirective therapy is concerned, it can be summated as a grotesque on psychoanalytic passivity. Its devotees aim to out-Caesar Caesar.

Nondirective therapy is, in effect, inconceivable. This so-called therapy is not really a therapy but only a game in which one of the players picks up and repeats the last few words spoken by the other as an inducement to continue the game.

12. Griesinger, W.: Mental Pathology and Therapeutics, translated from the German (Ed. 2) by C. Lockhart Robertson and J. Rutherford, London, New Sydenham Society, 1867, p. 59.

13. Griesinger,[12] p. 483.

All therapy must be, as all life is, goal-directed. The catch, of course, lies in whose goal is to be pursued and by what bearings the course is to be plotted. The current situation of the patient; his difficulties; the patterns of his past performances, successes, and failures; his own hopes and ambitions, all must serve as the coordinates by which the goals of therapy are to be charted. The therapist must scrupulously refrain from intruding upon the patient his own preconceptions and his unrelated therapeutic ambitions. Therapy must draw its ultimate goals from the realities and potentialities of the patient, and from none other. But without goals, without the sense and perspective of direction, therapy can only be a phantom march, a mere marking of time.

Schilder aptly phrased this issue [14]:

> It is the important task of the physician to develop the patient's personality according to the capacities, endowments, and characteristics of the patient. He (the physician) will be better able to do so if he has the conviction that the other human being is an entity of its own and is valuable in so far as it is a definite person.

Rado treats this matter even more pointedly.[15]

> The aim of psychoanalytic therapy is to increase the patient's capacity for enjoyment and active achievement in life by lifting him to a higher level of psychodynamic organization. . . . An adequate plan for modifying the patient's life performance must first consider the relation of available means to desired ends. It must include an itemized list of problems; an itemized list of tools; a set of instructions as to how to put the latter to work.

All this presupposes, nay, indeed, stipulates, not merely an uncovering of the past, essential but much overrated, but also an assessment of the current situation, the available resources, and the possible goals.

Here I needs must begin the summation of my exposition. The dynamics of the cure in psychotherapy, seen historically, reflects the emergence of diverse theories on the etiology of psychiatric illnesses. The older pre-Freudian theories are easy to comprehend. They are founded on limited, but valid, morbific causes. The amplitude and scope for specific psychotherapy which they inspired and allowed were likewise limited, and the dynamics of such therapy was simple and patent. With the advent of psychoanalysis the picture changed radically. Derived from an ingenious and intricate system of psychodynamics, the etiological theory of repression was advanced to account for much of general psychopathology, particularly of the psychoneuroses.

De-repression by the technique of free association was accordingly developed by Freud, and the dynamics of the psychoanalytic cure was spelled out in terms of "making conscious the unconscious, removing the repressions, and filling in the gaps of memory. . . . We do nothing more for our patients but enable this one mental change to take place in them; the extent to which it is achieved is the extent of the benefit we do them.[16]"

The etiological theory of repression and the dynamics of the psychoanalytic cure by free association I have subjected to critical analysis and evaluation.

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14. Schilder, P.: Psychotherapy, New York, W. W. Norton & Company, Inc., 1938, p. 166.

15. Rado,[11] pp. 50 and 51.

16. Freud, S.: Transference; in a General Introduction to Psychoanalysis, English translation of revised edition by Joan Rivière, New York, Liveright Publishers Corporation, 1935, p. 377.

The etiological theory of repression, while valid to some degree in much of psychopathology, and entirely adequate to account for certain given disorders, is nonetheless propounded in orthodox psychoanalysis with such catholic embrace as to prove ultimately erroneous in substance and corrupting in effect. It is erroneous when it ascribes to repression what is due to other causes, and it is corrupting because it impedes the appreciation of those other causes. I then analyzed the alleged uniqueness of free association, pointing out that it is essentially an exercise of the normal process of thinking and recall. What *is* unique to free association is the permissive atmosphere of the therapeutic relationship. This enables and encourages the patient "to be more candid with the physician than he ever dared to be with himself.[11]"

We thus come to the conclusion that the dynamics of the effective psychiatric cure embraces much more than de-repression by means of free association, even as most of psychopathology is traceable to much more than repression.

The dynamics of the psychiatric cure cannot, and must not, be cramped within a neat formula. It cannot be summated by a pat phrase. In reviewing the ascendency and decline, during the past 100 years, of the various theories on the etiology of psychiatric disorders, one cannot but be impressed with the fact that they were most in error where they sought singularly to account for all psychopathology, disallowing the validity and the pathogenic operations of other factors, propounded in other theories. It is at this point that I am impelled to bring up again the daemoniacal theory of etiology. This theory, as I observed, is sadly misunderstood, since it is confused with "witch hunting" and the "Christian Devil." In actuality, it impinges on the id of psychoanalysis and on the *élan vital* of Bergson. It was best propounded by the Greek philosopher Heraclitus, who wrote, "Ethos (ἦθος) is man's daemon." Unfortunately, this, even in translation, we now find difficult to comprehend, unless, of course, we try very hard, for, said Heraclitus, in the daemon there is a logos which connects knowledge of Being with insight into human values and conduct and makes the former include the latter.[17] There are a good daemon and an evil one, or, more precisely, the good daemon, as well as the logos, can be corrupted. But in the light of the good daemon, such a one as inspired Socrates, logos can comprehend the law divine, "the law by which all human laws are nourished.[18]" In recent decades we have experienced in the cruel totalitarianisms, both large and small, the sovereignty of evil daemons. In the contemporary vernacular, there can be no doubt that evil, corroding and corrupting "climates of opinion," can, and do at times, prevail, that they are noxious both to individuals and to the community, and that such evil climates of opinion may become manifest in psychopathology. Yet the fact must not be overlooked that essentially the primal daemon is good, and that it can give new life to conscious knowledge. Of this daemon it may be said what Mephistopheles said of himself—that it is "Part of the Power not understood, which always wills the Bad—and always works the Good.[19]" But this subject is far too complicated and involved to be treated at the end of a rather lengthy presentation. Let me, therefore, but round off this item by pointing to the radical change in social, cultural, moral, and esthetic values which our own times

17. Jaeger, Werner: Paedeia, New York, Oxford University Press, 1943, Vol. 1, p. 180.

18. Jaeger,[17] p. 181.

19. Goethe, J. Wolfgang: Faust, Part I, Scene iii.

have experienced and which I, for one, find sharply reflected in the difficulties of our contemporaries seeking psychiatric help.

Let me add that the psychotherapist who is not cognizant of the existence and of the operations of the daemon, or, knowing it, fears the daemon and thus cannot bridle *that* power which, willing the bad, always works the good—such a psychotherapist is indeed badly handicapped. He will never understand what is meant by prophylactic psychopathology. He will never really plumb the depths of the human psyche.

But, to return to the dynamics of the cure in psychiatry, I have said that no neat formula or pat phrase can summate it. Yet it is possible, and at this point I deem it my obligation, to name and to describe the principal components and the main operational sequences that are involved in the achievement of the psychiatric cure.

I shall begin with the patient. He is the primary factor in the dynamics of the psychiatric cure. His innate competences, his willingness to cooperate in the therapeutic process, the intrapsychic pressure which motivates and impels his quest for help, all these not only profoundly affect the ultimate issue but also influence and regulate the therapeutic process.

Freud, with his felicitous ingenuity in coining phrases, described the relationship of the patient to his therapist in terms of the transference neurosis. In essence, this means that the patient's attitude and behavior toward the therapist are of the same order as those which basically produced the untoward effects which brought him under therapy. How the therapist deals with the transference neurosis is crucial to the issue. Basically, he must be permissive. Unfortunately, some therapists consider this to be the alpha and omega of therapy. It *is* the alpha; it is not the omega! The patient is manipulatable. His competences, his willingness to cooperate, the intrapsychic pressure which he experiences, these are not absolutely given and inalterable. They are dynamic potentials which can be degraded or intensified; they are energy quanta which are convertible. The skilful and purposive manipulation of the patient's potentials is in effect the very essence of the art of the psychotherapeutic process. It is here that an appreciation of the daemon is a prerequisite, for without this appreciation the therapist is fearful and lost. He is compelled to yield the therapeutic initiative to the patient and he himself withdraw into the refuge of passivity.

This brings us to the second principal component of the therapeutic dynamics in psychiatry—the therapist. He not only must be informed in the data of psychiatry and skilled in the techniques of psychotherapy, but must, in addition, be "wise in the ways and meaning of life." It was Freud, I believe, who said that no therapist can bring the patient farther than he himself has gone. To be wise in the ways and meaning of life, the psychotherapist needs must know a great deal more than psychiatry. He needs must be a humanist both in learning and in being. In this an appreciation of the history of the profession and of his own specialty is most beneficial. The historical perspective induces humility, inspires hope, broadens one's vision, and teaches one to be earnest in enterprise, but not humorless in the face of reality.

Given the principal components, we can now turn to the operational sequence in which the dynamics of the cure in psychiatry becomes manifest.

Initially the patient comes to the psychiatrist with a complaint. The complaint is the patient's version of what "troubles him," or of "what *is* the trouble." Almost

always the version is wrong; that is, it does not conform to the objective reality. Despite that, it is imperative that the patient be encouraged and helped to formulate and to express his complaint. This is the first step in the anamnestic process. When the complaint has been well formulated, the second phase is entered upon—that of recitation and recall. In effect, this is a parade of the patient's history, given freely, amply, and in a measure repetitively. The patient's history may, will, and should deal with recent and contemporary experience, no less than with the past. The recitation and recall must be projected against the patient's complaint, to assess what, if any, relationship there may be between the one and the other. In this operation the therapist functions like an intelligent echo, giving back to the patient his very own words, but suggesting new contexts and new meanings. This process in time yields the third operation, namely, the reassessment and reorganization of the anamnestic material. A word must be said in amplification of this. In psychoanalysis, major emphasis has been placed on recall of forgotten and repressed material. Recall is both real and valuable but plays a less important role in the dynamics of the cure than the reorganization, i. e., the reassessment of remembered experience. The child, the young person, the immature and inexperienced young adult, remember well enough, but they all too often draw distorted and erroneous conclusions from their experiences. Such distortions and errors must be corrected. In this process the transference-countertransference effects of the therapeutic relation, as well as the extra-anamnestic effects, are of crucial import. What I intend by this can be summarized briefly. The patient can best reassess and reorganize his experiences with and under the guidance of the therapist. The terms interpretation and insight are applied to this process, but these are somewhat neutral designations. They do not reflect the powerful operations of that force which derives from "what the therapist stands for." Furthermore, and that is what I intend by extra-anamnestic effects, the patient cannot gain recovery and derive effective therapy solely from the contemplation—no matter how deep and detailed—of his past experience; for those ends he requires certain new experiences, which in a measure are derived from the actual person-to-person relationship of patient and therapist.

The final step in the operational sequences of the cure in psychiatry lies in implementing, motivating, and acting on the therapeutic gains. The psychoanalysts speak of this in terms of breaking, or terminating, the transference. This formulation places the emphasis on the patient-therapist relationship, with the initiative in the person of the therapist. It should, rather, be conceived in terms of the relationship of the patient to his immediate world, with the therapist endeavoring not to break the dependence but, rather, to dissipate it by encouraging the patient "to apply his gains in the real world"—to love Rome more, rather than Caesar less. This phase of therapy calls for the exercise of much skill and wisdom on the part of the therapist.

Such are the principal components and operational sequences that enter into the dynamics of the cure in psychiatry. Again, I need not elaborate what must be clear to all, i. e., that the listed steps and items are not, in actual operation, as distinct and sequential as they are given in the recitation.

Two of the eight etiological theories which I list at the beginning of my presentation I have not as yet touched on; these are the socioenvironmental and the ecological. Actually, however, I can do little more than mention them, for they are, so to say, at the peripheral zone of psychiatric research and study. Marxian econo-

mists and communist scientists have advanced the theory that much, if not most, of the psychiatric disorders are "economically determined." I can recall when Frankwood Williams, returning from a visit to Russia, enthusiastically reported that with the advent of the proletarian revolution there was a most remarkable drop in the incidence of the psychoses and neuroses. But that, of course, was a delusion. The relation of socioeconomic factors to the etiology, incidence, and issue of psychiatric illness is being studied, particularly in the United States, with fine discrimination and competent skills, by many men.

In these studies, psychiatrists, sociologists, anthropologists, ethnographers, and demographers are combining their skills and competences to assess the psychological effects of the socioeconomic matrix upon the individual and upon the group. We needs must await the issue of their studies. Yet even now we know that the social and economic components of the individual's environment can and do affect his personality, his sensitiveness to and tolerance of stress and frustration. Poverty, instability of the home, a degrading environment, the experience of being one of a minority-group which is socially not accepted, or is disparaged, all such experiences are in effect both traumata and deprivations and may contribute to manifest psychopathology. A plethora of the world's goods and operprotection, of course, can also contribute to the engenderment of psychological difficulties. The psychological effects of the social matrix are, however, subtler than these crudely patent instances show. The near future, I suspect, will teach us much on this score.

The ecological theory is, in effect, a much broader development of the thesis propounded in the socioeconomic theory. This concept is the modern counterpart of the Paracelsian micromacrocosmic picture. It has been sketched by James Halliday.[20] I myself [21] have attempted to formulate the ecological theory in several contributions on social medicine, and also in a chapter entitled psychosocial medicine. Fundamentally, the ecological theory holds that man is a creature of his own world, and, to put it somewhat cryptically, even as he does unto his world, so is it done unto him.

I wish to end this presentation by emphasizing one important factor. I have attempted to describe, to analyze, and to evaluate the principal theories on the etiology of psychiatric disorders current during the past 100 years and to deal with the dynamics of the psychiatric cure envisaged in each. It is most important to the scientifically guided physician to operate within the framework of a clearly defined theory of etiology and therapy; otherwise, he degenerates into an empiricist. With all that, however, it is important that he bear in mind that it is the man, the therapist, who avails and prevails—with, or against, the theory. In the ultimate, the dynamics of the cure derives more from him than from his theory. My own psychiatric mentor, A. A. Brill, was wont to say: "The most important factor in psychotherapy is the therapist." Experience certainly validates this dictum, which I urge you to bear in mind; otherwise, theory, intended as a supporting scaffold, is likely to become an imprisoning cage.

20. Halliday, James: Psychosocial Medicine, New York, W. W. Norton Company, Inc., 1948.

21. Galdston, Iago.: Psychosocial Medicine in Recent Advances in Psychosomatic Medicine, London, Sir Isaac Pitman & Sons, Ltd. 1953; Social Medicine and the Epidemic Constitution, Bull. Hist. Med. Baltimore, 1951; Social Implications of Dynamic Psychiatry: Social Medicine —Its Derivations and Objectives, New York, Commonwealth Fund, 1949.

CHANGES WITH AGE IN THE SPINAL CORD

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CHANGES in the body associated with age are receiving increasing attention in all branches of medical science. In view of the controlling influence which the nervous system exercises over all activities of the body, it seems highly important that the changes with age in this particular system should be given detailed consideration. Such consideration has been given to the brain, but the spinal cord, though scarcely less important, has not received a similar amount of attention. It was with this thought in mind that the present study was undertaken.

MATERIAL

The material for this investigation was selected from among the spinal cords which had been removed in the Section on Pathologic Anatomy of the Mayo Clinic. They were selected in such a manner that each decade of life was included. Spinal cords from 100 patients were studied. They were distributed among the various decades of life as follows: 10 from each of the first two decades, 5 from each of the third and fourth decades, 10 from the fifth decade, 15 from each of the sixth, seventh, and eighth decades, and 15 from the ninth and tenth decades combined. Sex was not considered. One strict criterion was observed in their selection, namely, that the patient had been free of signs and symptoms referable to the spinal cord. For example, all cases of encephalitis, meningitis, syphilis, pernicious anemia, multiple sclerosis, and traumatic myelitis were excluded.

The spinal cords were removed according to the method described by Kernohan.[1] They were preserved in a 10% solution of formalin. Sections for staining were taken wherever possible from the midcervical, midthoracic, and midlumbar regions. Transverse sections selected from these regions were stained with hematoxylin and eosin, with cresyl violet, and by a modification of Weigert's method. Longitudinal sections were cut in the sagittal plane close to the midline in such a way that some of the posterior columns were included. Such sections taken from these regions were stained according to the Orlandi modification of the Bielschowsky[2] stain or according to the method described by Bodian for staining axis cylinders.

ANATOMIC CONSIDERATIONS

Macroscopic Anatomy.—Gross atrophy of the spinal cord was stated by Campbell[3] to occur almost invariably in the 50 patients more than 60 years of age whom he studied. However, other workers have not found this to be prominent, and in the few cases in which I had an opportunity to make examination atrophy of the

1. Kernohan, J. W.: Removal of the Spinal Cord by the Anterior Route: A New Postmortem Method, Am. J. Clin. Path. **3**:455-458 (Nov.) 1933.

2. Bielschowsky, M.: Histopathology of Nerve Cells, in Cytology and Cellular Pathology of the Nervous System, edited by W. G. Penfield, New York, Paul B. Hoeber, Inc., 1932, Vol. 1, p. 174.

3. Campbell, A. W.: The Morbid Changes in the Cerebro-Spinal Nervous System of the Aged Insane, J. Ment. Sc. **40**:638-649, 1894.

spinal cord was not remarkable. The spinal cords in many of the cases had been in fixative for many years. Unless an observation of this kind is correlated with weight, height, and bony structure, the conclusions drawn may be misleading.

Osseous deposits on the spinal arachnoid had been observed by Campbell, and in a case later described by Sander [4] the entire spinal cord was encased by calcareous deposits. Herren [5] has recently studied the occurrence and distribution of calcified plaques on the spinal arachnoid in man. These plaques were commoner in the aged, but they were found occasionally in young people. Herren stated that the calcium was a product of deposition rather than the result of osteogenesis. I observed calcareous deposits on the posterior surface of the spinal cord in two patients who were over 70 years of age.

Critchley,[6] in his review of the literature dealing with the neurology of old age, commented on the thickening of the meninges of the aged. Naka [7] observed in one of his patients that the pia and the arachnoid were matted together. Thickening of the meninges was not an outstanding feature in my cases.

Arteries and Arterioles.—The degree of thickening of the arterial wall was noted, but a detailed study of the cytologic changes in the vessels did not come within the province of this study. Arteriosclerosis was not found in the first three decades of life, and in the fourth decade only two patients showed a mild degree of arteriosclerosis. Neither patient had had hypertension. After 40 years of age thickening of the vessels became more evident and was present in a mild degree in 9 of the 10 patients in the fifth decade.

The number of patients in the succeeding decades who showed marked evidence of arterial change was much greater. Some degree of arteriosclerosis was consistently present, and the more prominent changes were in those patients who had had hypertension. It should be noted, however, that mild and moderate degrees of arteriosclerosis were present in 15 of 18 patients in the last seven decades in whom there had been no evidence of hypertension.

The vessels in the posterior columns were more severely affected by arteriosclerosis than the vessels in other portions of the spinal cord. The arterioles were much more prominent in the later years of life than in the earlier years. This prominence was explained by the presence of a thickened wall and much hyaline change in the adventitia and the periadventitial substance. In the arterioles of patients with severe hypertension the media of the vessel wall was much hypertrophied, but this was not prominent in the majority of the other patients.

The literature dealing with arteriosclerosis of the spinal cord from the standpoint of pathologic anatomy is very meager. Cobb and Blain,[8] in their review of arteriosclerosis of the central nervous system, commented that the spinal cord is much

4. Sander, W.: Das senile Rückenmark mit Demonstration, Neurol. Centralbl. **18**:954-956 (Oct. 15) 1899.

5. Herren, R. Y.: Occurrence and Distribution of Calcified Plaques in the Spinal Arachnoid in Man, Arch. Neurol. & Psychiat. **41**:1,180-1,186 (June) 1939.

6. Critchley, M.: The Neurology of Old Age, Lancet **1**:1,119-1,127 (May 23); 1,221-1,230 (June 6) 1931.

7. Naka, K.: Die pathologische Anatomie des senilen Rückenmarkes, Arch. Psychiat. **42**:604-614, 1907.

8. Cobb, S., and Blain, D.: Arteriosclerosis of the Brain and Spinal Cord, in Arteriosclerosis, edited by E. V. Cowdry, New York, The Macmillan Company, 1933, pp. 397-429.

less frequently the site of this process than the brain. Campbell's and Sander's independent studies, however, draw attention to the frequency with which some type of change in the arteries takes place in the spinal cord of the aged. The studies of Kelly [9] (1896) and Naka (1907) are in agreement with this. Keschner and Davison,[10] in 1933, observed thickening of the vessels of the spinal cord and in some instances obliteration of the lumina. Furthermore, in one case they noted that sclerotic changes in the posterior spinal arteries were greater than in the anterior spinal arteries. The present work confirms that of these earlier workers. Stern [11] (1936) found only fibrosis of small arteries and stated that pronounced arteriosclerosis of the spinal arteries is rare.

Gliosis.—The neuroglial tissue increases in old age, and this increase is mainly the result of hypertrophy and proliferation of the astrocytes. In some cases this becomes so pronounced as to be worthy of the designation gliosis. This was studied in sections stained according to the phosphotungstic-acid hematoxylin method of Mallory.

Changes in the neuroglia in the first five decades were insignificant. In 1 of the 10 patients in the second decade mild gliosis of the fasciculus gracilis was present. This patient had suffered from chronic ulcerative colitis for many years. The explanation is offered that in this case poor nutrition or toxemia over a long period may have been a causative factor in producing atrophy of the nerve fibers and gliosis in the same region.

After the age of 50 this change was commoner. Gliosis of the fasciculus gracilis of the spinal cord was observed in 6 of the 15 spinal cords in the sixth decade, in 8 of 15 cords in the seventh decade, and in 12 of 15 in the eighth decade (Fig. 1). In the combined group of the ninth and the tenth decades, all spinal cords showed this alteration. In two cords in the eighth decade it was more prominent than in the other spinal cords examined. Gliosis was not present to any extent in other regions of the spinal cord. Students of this subject around the turn of the last century found gliosis rather more widespread than I did in my study. It is quite possible that social advances in medical science may account in part for this difference. For example, it is not unreasonable to ponder the possibility that many symptoms ascribed to senility may have been due to nutritional disorders. I wish to emphasize that if gliosis is present to a pronounced degree, some cause other than senility ought to be sought as its explanation.

Sander [4] observed in aged subjects gliosis secondary to the degeneration of the nerve fibers. Pic and Bonnamour [12] and Naka [7] commented on gliosis in the spinal cords of the aged and noted its predilection for the posterior and lateral columns. It was especially prominent around blood vessels. Flügel [13] found much the same thing as the result of his investigation. Stern,[11] as the result of his work, came to

9. Kelly, A. O. J.: Senile Paraplegia, J. Nerv. & Ment. Dis. **23**:717-721 (Nov.) 1896.

10. Keschner, M., and Davison, C.: Myelitic and Myelopathic Lesions: III. Arteriosclerotic and Arteritic Myelopathy, Arch. Neurol. & Psychiat. **29**:702-725 (April) 1933.

11. Stern, K.: Beitrag zur Histopathologie des senilen Rückenmarks, Ztschr. ges. Neurol. u. Psychiat. **155**:543-554, 1936.

12. Pic, A., and Bonnamour, S.: Des troubles médullaires de l'artério-sclérose: la parésie spasmodique des athéromateux, Rev. méd. **24**:104-133 (Jan.) 1904.

13. Flügel, F. E.: Quelques recherches anatomiques sur la dégénéresence sénile de la moelle épinière, Rev. neurol. **1**:618-623 (May) 1927.

somewhat different conclusions. He found proliferation of the neuroglia in the marginal area, in the region of the central canal, in the dorsomedial fields of the gray substance, and in the posterior columns. It was his belief that the proliferation of the glial fibers was independent of vascular change.

Atrophy of the Nerve Fibers.—Sections of the spinal cord prepared according to the method of Weigert were examined and areas of demyelination noted. It is interesting and worthy of comment that it was difficult to find a section which would meet all the requirements of normality. Duncan [14] mentioned that he encountered this difficulty in attempting to find suitable sections for teaching purposes. Artifacts were not uncommon, and therefore care had to be exercised in the interpretation of sections stained according to the method of Weigert. Weil,[15] in his textbook, has drawn attention to these problems.

Fig. 1.—Photomicrograph of the tips of the posterior columns in the cervical portion of the spinal cord (stained with Mallory's phosphotungstic-acid hematoxylin method) of a man aged 79. Note the gliosis in the tips of fasciculus gracilis. × 85.

With the exception of the spinal cord in the case already mentioned, in which there were gliosis and atrophy of the nerve fibers in the posterior columns, there was no instance of this phenomenon in the first five decades of life. Spinal cords of the patients in the sixth and seventh decades showed a mild degree of pallor of the posterior portion of the fasciculus gracilis, appearing in 7 of the 15 cords examined in each decade. This pallor, on the basis of Weigert's stain, represented atrophy of the myelin sheaths in that region. A similar state of affairs existed in the spinal cords of the patients in the eighth, ninth, and tenth decades, though a larger number were so affected. All the spinal cords of the eighth and ninth decades showed evidence of slight demyelination in the fasciculus gracilis, and it was somewhat more pronounced in one instance than in the others (Fig. 2).

14. Duncan, D.: Incidence of Mild Degrees of Atrophy in the Fasciculus Gracilis, Arch. Path. **26**:664-675 (Sept.) 1938.

15. Weil, A.: A Textbook of Neuropathology, Philadelphia, Lea & Febiger, 1933, p. 30.

Nearly all workers mention some degree of demyelination in the spinal cords of elderly people. Campbell and Naka, in independent papers, have given attention to the evidences of degeneration of this type as they saw them in the sections stained according to the method of Marchi. Many authors have stated that the posterolateral columns were the main regions involved in this process of demyelination. The results of my examinations indicate that the fasciculus gracilis is much more affected than the lateral columns or even the fasciculus cuneatus. Sander, on the basis of an analysis of 30 spinal cords, divided the phenomenon of degeneration into three types according to the degree of demyelination. In his first type there was a mild involvement of the nerve fibers, which might be in special tracts or limited to one part of the spinal cord. This, he believed, was simply a part of physiologic senility. In the second type the periphery was more affected than the center. This type received the designation of marginal degeneration. Under the third type he classified those cases

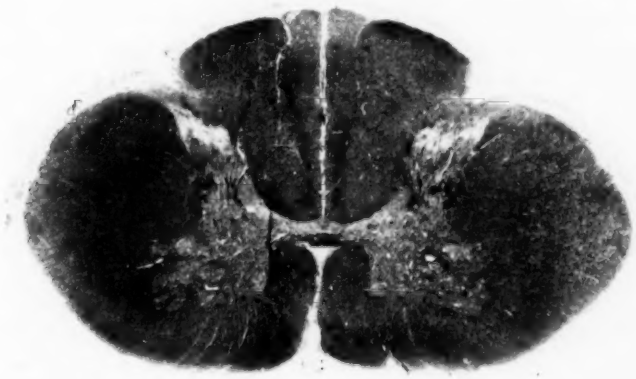

Fig. 2.—Photomicrograph of the cervical portion of the spinal cord (stained according to the method of Weigert) of a man aged 82. Note the pallor in the area toward the periphery of the fasciculus gracilis, representing atrophy of the nerve fibers in this location. × 7.

in which there were apparent wedges or half-moon-shaped patches of degeneration, and it was in these regions that the gliosis already commented on became most pronounced.

Duncan [14] has made the most recent contribution to this phase of the subject. In a series of cases, he found that in about 50% of people more than 60 years of age the fasciculus gracilis in its posterior portion appeared pale when stained according to the method of Weigert. He regarded this pallor as a loss of myelin sheaths in this location.

Axis Cylinders.—The axis cylinders of the spinal cord were examined in each case in longitudinal sections stained according to the method of Orlandi or Bodian. There was considerable variation in the thickness of the axis cylinders within the same area in any given section. Some axis cylinders had a wavy outline and occasionally presented localized swellings on their borders. Features such as these were not common in the spinal cords of the patients in the first three decades of life, but they occurred not infrequently in the spinal cords of persons in the later decades.

Localized swellings on the axis cylinders were interpreted as evidence of degeneration. Axis cylinders in the process of degeneration were found more frequently toward the periphery of the spinal cord. Corpora amylacea appeared to encroach on the axis cylinders in some instances. Satisfactory methods for staining axis cylinders have not been available until recent years; consequently, many details of the variation in their normal structure remain to be studied. Swelling of the axis cylinder, particularly irregular areas of thickening, have been considered in the textbooks to be evidence of degeneration.

Ganglion Cells.—The ganglion cells were examined carefully in sections stained with cresyl violet and, again, in the ordinary hematoxylin-eosin-stained sections. In studying the ganglion cells, allowance must be made for certain variations in the reaction of different cells to the stain. This variation occurred not only in different sections but within the same section. In some sections the pericellular spaces were larger than in others. However, the pericellular spaces seemed significantly larger only in the spinal cords which had been taken from infants.

Pyknosis and chromatolysis in the cells of the ventral horn did not occur frequently, and in no instance were they pronounced enough to be of any significance. It should be kept in mind that a paucity of cells in the ventral horn of a section of the spinal cord does not necessarily mean fewer ganglion cells in this section. It frequently means that the section may have been taken through a region in which there were normally few cells, since the ganglion cells have a pseudosegmental arrangement around blood vessels.

The ganglion cells as observed in the cords of the first two decades were essentially the same in all respects. "Pigment atrophy" was present in the anterior horn cells of three of the five spinal cords of the third decade. The same change was observed in the cords of the fourth decade, being moderately severe in one and scarcely visible in two others. In spinal cords of the fifth decade, "pigment atrophy" of the ganglion cell was a constant finding, though varying in severity. The cells of Clarke's columns were affected, too, by this process. Not all the ganglion cells were involved, and the degree of "pigment atrophy" varied greatly in different cells.

The last five decades of life may be considered together, as the findings were much the same in each decade. As one would expect, some cells of the spinal cords of patients in the 5th decade showed a greater degree of "pigment atrophy" than some of those of patients in the 10th decade. On the whole, there appeared to be a progressive increase in the degree of "pigment atrophy" with advancing years. In fact, if "pigment atrophy" were to be considered an abnormality, one could not find a normal spinal cord after the age of 40, and by the seventh and eighth decades scarcely a normal ganglion cell could be found (Fig. 3). In some cells the change was so severe that the cell appeared as a pyknotic pigment spot.

Investigations into the nature and origin of "pigment atrophy" have not been very enlightening, though this type of change has been recognized for a long time. Campbell expressed the opinion that hyperpigmentation of the nerve cells was characteristic of old age. Bielschowsky stated that even under normal conditions pigment may occupy considerable space in the cell body of senile persons. Campbell suggested that the pigment might be altered fat. According to the studies of Borst and Hueck,[16] in 1912, it is a lipofuscin, which consists of a mixture of phosphates, cerebroside,

16. Borst and Hueck, cited by Bielschowsky.[2]

and cholesterol esters. Recent researches by Altschul [17] have not completely clarified this subject. He expressed the opinion that the pigment may be a "food" which is not used up when the ability of the nerve cell to function is reduced. Thus it becomes stored in the cytoplasm of the cell and eventually appears as an increased pigmentation. Bielschowsky [2] pointed out, as did Altschul again, that this pigment may be increased in certain diseases.

Campbell and many other authors have commented on the good condition of the gray matter in the spinal cords of the aged. Sander's work and that of Flügel, many years later, are not in entire accord with this view. Sander found the cells in various stages of degeneration in many elderly persons. Flügel stated that many cells of the anterior horns were pyknotic and that some had a great increase in pigment. His most interesting observation, however, was in finding cells of the spinal cord in two patients that showed the classic alteration of Alzheimer. These particular cells con-

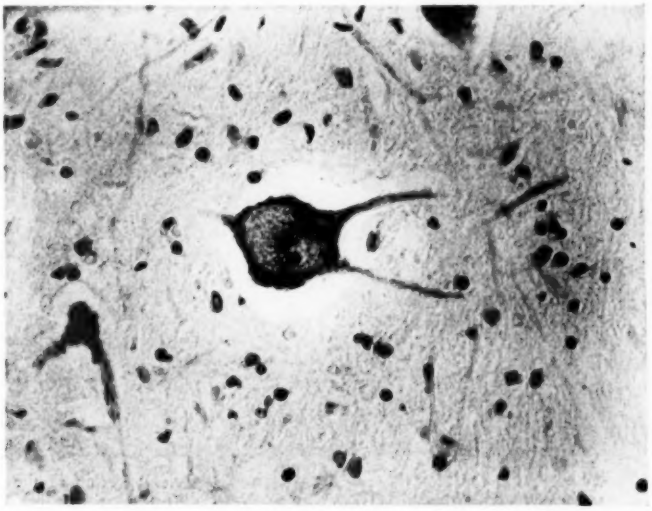

Fig. 3.—Photomicrograph of a ganglion cell (stained with cresyl violet) showing "pigment atrophy" in a cell of the ventral horn of the cervical portion on the spinal cord of a male aged 65. × 350.

tained a dense network of disorganized fibrils coiled on themselves. He stated that this finding had never previously been reported, and my own search of the literature confirmed this statement. Stern observed a diminution of cells high in the thoracic and cervical segments of the spinal cord.

Corpora Amylacea.—Corpora amylacea were first described by Purkinje [18] in 1837. Their presence in the brain has been the subject of much more study than their relation to changes in the spinal cord with age. The substance of corpora amylacea is amyloid-like, but it is generally recognized that corpora amylacea are different from other substances found in the human body containing amyloid. All

17. Altschul, Rudolf: Über das sogenannte "Alterspigment" der Nervenzellen, Virchows Arch. path. Anat. **301**:273-286, 1938.

18. Purkinje, cited by Critchley.[6]

authors agree that corpora amylacea occur chiefly near blood vessels or ependymal and glial surfaces. Rasmussen,[19] in his study of the eighth nerve, observed that corpora amylacea were associated with the glial tissue. At the point where the neuroglia ceases, corpora amylacea are no longer found along the course of the nerve. Thus it would seem reasonable to conclude that at least neuroglia is essential for the production of these globular bodies.

Ferraro and Damon,[20] in 1931, reviewed the literature concerning corpora amylacea. In this review they carefully enumerated and commented on the various hypotheses which have been brought forward to explain the origin of these bodies. They cited evidence in their paper in the form of photomicrographs to illustrate the alterations which take place in the nuclei of the oligodendroglia and microglia cells as they are transformed into corpora amylacea. Mutalimow,[21] in 1933 attempted to prove the cellular origin of corpora amylacea by showing that they contain

Fig. 4.—Photomicrograph of the posterior columns of a cervical portion of the spinal cord (stained with hematoxylin and eosin) of a woman aged 65. Note the large number of corpora amylacea. × 95.

nuclein. Biggart,[22] in 1949, expressed the opinion that, whatever their origin, their presence indicates some degree of atrophy of parenchymatous tissue. Saxen,[23] in 1937, stated that they arise from axis cylinders through the degenerative and regenerative metamorphosis of these structures. For the present, their origin is still open to further investigation.

19. Rasmussen, A. T.: Studies of the 8th Cranial Nerve of Man, Laryngoscope **50**:67-83 (Jan.) 1940.

20. Ferraro, A., and Damon, L. A.: Histogenesis of Amyloid Bodies in the Central Nervous System, Abstracted, J. Nerv. & Ment. Dis. **73**:206-209 (Feb.) 1931.

21. Mutalimow, B.: Über Corpora amylacea des Zentralnervensystems, Centrabl. allg. Path. u. path. Anat. **57**:119-121 (April) 1933.

22. Biggart, J. H.: Pathology of the Nervous System: A Student's Introduction, Ed. 2, Baltimore, Williams & Wilkins Company, 1949, p. 21.

23. Saxen, A.: Über die Genese der Corpora amylacea im Zentralnervensystem, Virchows Arch. path. Anat. **300**:534-559, 1937.

Corpora amylacea were not found in any of the spinal cords of patients less than 30 years of age. In the fourth decade slightly more than half the spinal cords had a few of these bodies scattered around the surface of the cord. They were most commonly found around the entrance of the posterior roots, though a few were seen in the posterior columns, and even occasionally in the ventral horns.

All the spinal cords of patients more than 40 years of age had a few corpora amylacea. In the fifth decade they were not very conspicuous, and in some instances a prolonged search was necessary to find them. Their number varied from 1 or 2, which could be seen around the entrance of the posterior roots, to 10 or 20, which might be seen scattered throughout the section. In the next decade, in all but two cords, they were more numerous than in the previous age group. In four cords of the seventh decade corpora amylacea were few; in the remaining cords they were more evident, and in two of these they were very numerous. From the eighth decade there were two spinal cords in which they were few; in the rest they were prominent, and on the average they tended to exceed the quantity found in cords of the seventh decade. Corpora amylacea were very numerous in one cord of the ninth decade, and in the remaining cords of this decade they were moderately numerous. It is interesting that in one cord of the 10th decade the number of corpora amylacea was minimal, whereas in the other two cords they were prominent, and in one of these very prominent (Fig. 4). It can be stated with assurance that, although there is considerable variation in the quantity present in any one decade, their number in the respective sections increases with age.

COMMENT

The histologic changes which occur in the spinal cord as an accompaniment of the aging process are doubtless of some significance. However, it is difficult to correlate them with the clinical condition of the patient in many instances. Any attempt to explain the origin of these changes is fraught with even greater difficulty. It has long been thought that the changes with age occurred as the result of a diminished blood supply; the latter, in turn, was considered to be due to arteriosclerosis. To bring forward evidence to the contrary is not an easy matter; yet I should like to suggest that the aging process is inherent in the cell itself, in the same way that growth is.

As the result of my investigation, I was unable to find any positive correlation between certain changes which were apparently the accompaniment of age and the degree of arteriosclerosis present. However, recent studies confirm earlier impressions that the white matter of the spinal cord has a poorer blood supply than the gray matter and that the lower portion of the spinal cord is not as well nourished as the upper. These facts become significant when it is pointed out again that from a clinical, as well as from an anatomic, point of view these regions are the ones most affected. Such variations in the blood supply may help to explain the degree of changes in the aforementioned regions; yet they do not explain the factor or factors which initiate the change.

In connection with atrophy in the fasciculus gracilis, some mention should be made of the study of the eighth and ninth thoracic nerve roots by Corbin and

Gardner.[24] They counted the myelinated fibers in the eighth and ninth spinal nerve roots and found a gradual loss of fibers after the third decade, amounting to a 32% decrease, in a patient 89 years of age. They expressed the opinion that this was the result of death of spinal ganglion cells and suggested that it might account for the decrease in the vibratory sensibility found in later life. Be that as it may, for our purposes it is important to remember that the death of a ganglion cell and the loss of a nerve fiber in the dorsal root mean loss of a nerve fiber in the posterior columns and that in the case of the lower nerve roots this means a loss of fibers in the fasciculus gracilis.

Davison and associates[25] have reported two cases of atherosclerotic myelopathy with syrinx formation. Both the patients had marked clinical symptoms and histologic evidence of atherosclerosis in the vessels of the central nervous system. Observations during the course of our work would raise some doubt as to whether atherosclerosis was the primary cause of the syrinx formation. We observed rather marked arteriosclerosis in the spinal cords removed from patients who had severe hypertension; yet there was no syrinx formation to be found or clinical phenomena to be noted.

Andrew,[26] in his study of the aging of nerve cells, noted changes in cell outlines, loss of Nissl material, changes in the nucleus, and granulation of the Golgi apparatus. O'Leary,[27] in speaking of the aging process in the nervous system, calls attention to the dearth of specific knowledge of chemical processes involved. He cites several ways in which the enzymatic process may be disturbed. Endogenous and exogenous toxins and nutritional factors have to be considered.

SUMMARY

An attempt has been made to study the changes which take place in the spinal cord from birth to old age. It has not been possible to explain the nature of the changes; in fact, such an explanation involves the whole general problem of aging. The significant changes are summarized in the following paragraph:

In infancy the spinal cord is characterized by a rather more gelatinous consistency than in adults. Microscopic study of the tissue at this period in life revealed that there were large spaces around the ganglion cells and the blood vessels. The whole appearance of the spinal cord was distorted. These findings were due to fixation of tissues in which there was an excess amount of fluid. This is characteristic of the tissues of infants. After the first five years of life the appearance of the cord and its consistency showed very little change. Ganglion cells, nerve fibers, and interstitial tissues did not give any evidence of a degenerative process. Changes became increasingly frequent and more obvious from the age of 30 to that of 60 years.

24. Corbin, K. B., and Gardner, E. D.: Decrease in the Number of Myelinated Fibers in Human Spinal Roots with Age, Anat. Rec. **68**:63-74 (April) 1937.

25. Davison, C., Brock, S., Goodhart, S. P.: Atherosclerotic Myelopathy with Syrinx Formation: Differentiations from Other Types of Syringomyelia, Arch. Neurol. & Psychiat. **50**:565-574 (Nov.) 1943.

26. Andrew: in Cowdry, E. V.: Problems of Aging, Ed. 3, Baltimore, Williams & Wilkins Company, 1952.

27. O'Leary: in Cowdry's Problems of Aging, Ed. 3, Baltimore, Williams & Wilkins Company, 1952.

Arteries and arterioles were thicker and had narrower lumina, though this was not a constant feature, as has already been pointed out. Slight demyelination in the posterior portion of the fasciculus gracilis occurred occasionally and was usually accompanied by gliosis. Gliosis and demyelination of the fasciculus gracilis first made their appearance in the sixth decade. "Pigment atrophy" of the ganglion cells was observed at this period in life and in the succeeding decades. Corpora amylacea occurred in a few spinal cords of the fourth decade and in every cord of the fifth and sixth decades.

After 60 years of age the particular characteristics just described for the period of middle life were much more apparent and more constant. Chalk-like deposits were found on the surface of the spinal cord in two cases. Though such deposits may occur in younger people, I did not observe them. Changes in the arteries were much severer. "Pigment atrophy" in the ganglion cells was much more prominent and affected a larger number of cells. Demyelination of nerve fibers in the fasciculus gracilis was very common and was accompanied by mild gliosis. Corpora amylacea occurred in much larger numbers around the posterior roots, posterior columns, blood vessels, and pial surfaces. The photomicrographs are selected to show the most prominent changes seen in the cases studied. It is apparent that these changes are not severe and probably gave no significant signs or symptoms. I wish to emphasize that, if marked demyelination, widespread gliosis, or severe degeneration of the ganglion cells be observed, very careful search should be made for some explanation other than the aging process.

RELATION BETWEEN PERSONALITY FACTORS AND FATIGUE IN SEVERE POLIOMYELITIS

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POLIOMYELITIS is a disease about which relatively little is known. Every possible method of inquiry should be included in the effort to understand the wide variety of puzzling clinical aspects of this disease.

This paper presents information gathered in a study of the personalities of 14 patients, ranging in age from 14 to 35, who were admitted to the respirator unit of the Children's Hospital School. The study of this series of patients happens to have brought out a rather remarkable similarity of attitudes characterizing most of these patients. What stands out in the composite life story of this group is an unusual lack of aggressive self-assertiveness, associated with a compulsive need to please other persons and a constant fear of failure, driving the patient to extreme overexertion. In a later section, the possible bearing of these observations on the course of the poliomyelitis will be discussed, but before doing so it will be useful to present briefly the salient features of these cases.

CASE PRESENTATIONS

CASE 1.—*Housewife and research worker; age 27.*

The patient stated: "I never argue. I don't fight. It just isn't my nature. I do everything quickly." Mrs. Y. was positive about the effect of the fatigue factor. She said: "I can tell you exactly why I was tired. I had gone to my grandmother's funeral from Washington to a mid-western state. We got into a car and drove without even trying to sleep. My grandmother died on a Thursday. We got to my home town on Friday (midnight), then got up at 6 a. m. and drove 200 miles to the funeral, then drove back. We got to bed at 3 a. m. (Sunday), and I was up at 6 a. m. to go to 7 o'clock Mass. We left at 11 a. m. [Sunday] and arrived in Washington at 4 p. m. on Monday (Labor Day). I went to work on Tuesday (Sept. 4). [The patient was doing research for the Government. She recalled, "It wasn't a cinch. We were writing a day-by-day account of the war."] On Wednesday the patient had generalized weakness of both legs. The following day (Sept. 6) she experienced respiratory distress, progressive paralysis of the abdominal muscles developed, and she required respirator care.

When asked why she had "hurried" back to work, the patient replied, "I didn't like missing work. There are too many loafers in the Government."

Mrs. Y. described her home life as being harmonious. She was a twin. She said that her twin sister was more "gregarious," was "happy-go-lucky," and had a "terrific temper." Mrs. Y. added, "I don't believe I have a temper." She had suffered from severe dysmenorrhea and chronic constipation and had "felt dead-tired" for several years preceding the onset of her poliomyelitis. An older sister and a younger sister were both described as being "full of pep and as having average tempers."

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CASE 2.—*A Negro farmer; age 35.*

The patient was a soft-spoken, self-effacing Negro, who stated: "I always try to do right. I never liked to argue." He had worked as a farm hand and at odd times helped to pour concrete. He was married, had two children, and was well adjusted at home. In January, 1945, he began working from dawn to dusk in order to save enough money to buy a farm. The Negro who owned the farm "just took it easy," while the patient "did all the work." In addition to his heavy farm duties, he began to cut cord wood (September, 1945); then, a few weeks later, he harvested the crops. The patient was pleased with himself, looked forward to receiving his share of the profits, and felt that he was well on his way toward owning a farm of his own. The harvest chores were completed on October 2. Four days later he experienced occipital pain and weakness of both legs and was in a respirator on October 11.

CASE 3.—*Dentist; age 32.*

The patient described himself as being a "very conscientious" person who "hated to argue with anyone." He was an only child, who "always was very obedient." He recalled, "I tried to take care of everyone in trouble. I couldn't say 'no' very well, and I couldn't do sloppy work. I would worry over each piece of bad work."

The patient was married and had three healthy children, and his home life was harmonious. In October, 1946, a month before the onset of the illness, he fell behind in his work because he had "to redo the work on four dental plates." This was very irritating to a meticulous person who already was working 10 hours a day, six days a week, trying to keep up with a busy dental practice. For the three months preceding the illness the patient had been exceptionally busy, but with additional overtime he finally caught up with his work. He was feeling very "good," when, a week later, on Nov. 23, a "kink" in the back, vomiting spells, and leg pains developed, and he was in a respirator on Nov. 26.

CASE 4.—*Farmer; age 21.*

The patient stated: "I never liked to argue." . . . At school, when the boys used to push me around, I took it. I was smaller and never liked to fight. I hated mathematics and was determined to make good on my father's 300-acre farm and began to work 'hard.' . . . I worked very hard. I really did. I dug in. It was just my parents and I. It was more work all the time. My mother used to tell me I was working too hard."

By the spring of 1944 the patient was feeling "too tired" to go out in the evening. In spite of all this "hard" work, there was a constant anxiety about the possibility of failure, which the patient ascribed to a lack of modern farm machinery. He continued to work diligently and completed the haying, which was "the hardest and hottest" part of his chores, during the first few days in August, 1944. He was "glad that the worst was over," when his paralysis began, on August 5, and progressed to quadraplegia, with respiratory distress, requiring emergency care.

CASE 5.—*School boy; age 14.*

The patient was a husky boy who liked athletics and hated to be indoors. He found it difficult to assert himself and stated that he had never "sassed" his parents, adding, "That's one thing I won't do, that is, to criticize somebody or get angry with them." He had felt frustrated in the fifth grade (at the age of 11, in 1944) because he found it difficult to go to his teachers for help in his school work. The following year he resented the rigid discipline of another school, where he had been "slapped" while he was doing his best.

In May, 1945 (at the age of 12) he was informed that he had an "athletic heart" and was compelled to give up all sports. The patient felt "terrible," as he had his "heart set" on making the basketball squad. He had played center, when he was "shoved around," he was never able to feel "mad and never pushed back."

The patient had an unhappy summer (1946) in a camp, where he was not permitted to participate in athletics. He looked forward to entering a county high school, where "the teachers were very understanding and you could go to them after school and they would explain anything that you didn't understand." He entered this new school with high expectations on September 11, and on September 16 he had onset of poliomyelitis [1] and was home for one month. He returned

1. This history is extraordinarily atypical of acute poliomyelitis.

to the same school the latter part of October, although his legs were "still weak." He worked "extra hard" after school hours in order to make up the time which he had lost. On Nov. 10 his back began to hurt and both lower extremities were paralyzed, and on Nov. 13 he was in a respirator.

CASE 6.—*Office executive; age 23.*

The patient was an energetic, anxious-to-please person. He was on the high school track, soccer, and baseball teams. He had worked after school whenever possible and had "never liked to ask his parents for money," preferring to make his own. His mother had died when the patient was 8 years old; he was very fond of his stepmother. There is a younger half-brother.

He never liked an argument, saying, "I'd rather concede than get into an argument." The patient was discharged from the Navy in 1945 after three years' service. He had married in 1944 and described his wife as being "perfect"; their baby was born in 1945.

During the year preceding the illness the patient was a cheerful, conscientious worker who made a fairly good salary but did not think that he had a good future in selling vacuum cleaners. In June, 1945, he found just the job with the future that he had "dreamed about." It was as an assistant to an executive in an oil corporation. The patient recalled, "I worked pretty hard, putting in a lot of nights at home. I knew I had a good job, and I wanted to get ahead. I was anxious to make good." On his nights off he played ball "for fun." In spite of the extra work, the patient found himself falling behind; so he began working even "harder." He stated, "We had more work than one person could do. After working nights, I finally caught up. I felt good. I was very well pleased with myself.

A week later (Aug. 25) he had onset of severe headache, stiff back, pain and weakness in both legs, and paralysis of the diaphragm, requiring respirator care.

CASE 7.—*High school girl; aged 19.*

The patient was an outwardly happy person who referred to herself as being a "worry wart." She "hated to argue," saying, "I just give in." She was always afraid that she would fail every examination, although her marks had been satisfactory all through high school. She was having "an awful hard time" with English and was struggling with extra homework and additional coaching. Although she studied diligently, her marks remained low, and she "tried to work even harder." The patient had "gone out all the way" for athletics, was in the senior play, and was class treasurer. By May, 1945, she was feeling "very tired." She continued her strenuous extracurricular activities, although at times she would feel "limp" and was admonished by her mother for "overdoing things." During the week preceding her examinations the patient had more time for tennis.

The dreaded final examinations in English were to begin on June 9. She took her first, and easiest examination, on June 3. The following day she was febrile and complained of headache. Hospitalization occurred on June 7, and paralysis of all extremities, abdominal muscles, and diaphragm was noted.

The patient said, "I was just beginning to prepare for English, my hardest subject, when I took sick. I dreaded all my examinations. They all scared me."

CASE 8.—*School girl; age 15.*

The patient was a good golfer (her father is a professional golfer) but preferred riding her horse and swimming. Her mother reported that the patient "hated indoor work and was crazy about the outdoors." Nevertheless, she always did her best in school. She disliked arguments, preferring to give in, and said, "I'd rather do things for people than have them do things for me." In March, 1946, the parents moved from Florida to Maryland. The patient was left behind to take special examinations in May in order to get full credit for completing the eighth grade. She recalled, "I always worked hard in school, but this was extra hard work. It was awful hot, and I also was worried whether my horse would be able to leave with me." The school tests were completed on May 15, and arrangements were made to send the horse with her. The patient was relieved that her troubles were over. The illness began on May 19, and on May 23 she suddenly had great difficulty in swallowing and phonating. The neck muscles, left arm, and muscles of respiration were paralyzed, necessitating emergency respirator care.

CASE 9.—*College girl; age 22.*

The patient appeared to be well adjusted and "easygoing." She said that she disliked to argue and hated "sloppy work." After completing her sophomore year at college, she immediately went to work as a secretary in a large Eastern university. The patient was not too sure of herself and found the work difficult. She was especially worried about her slowness in taking shorthand and said, "I was upset that so many things had to be done that I couldn't be as neat as I wanted to be." She would come home tired and worried, and found that keeping her apartment in order took a great deal more work. Her state of tension increased; she recalled, "This was the first time that I felt that things depended on me, and there were so many things to keep straight. I worried about my poor vocabulary and that I'd get behind whoever was dictating." She also said, "The two weeks before I became sick I felt more certain. I found it was not so hard and that people don't dictate so fast. I had been preparing for 100 words a minute." She summed up her attitude by saying, "I had felt uncertain, but I was getting over my uncertainty when I became ill" (on July 28, 1944).

CASE 10.—*Housewife (sister of Patient 11); age 25.*

The patient enjoyed working with her hands and "never liked being waited on." Her compulsive need to do everything for herself was considered as a need "to be independent." In 1941 the patient failed college chemistry; later that year she was frustrated in a love affair and became depressed. She married in 1943, was soon pregnant, and felt "cheated out of a period of adjustment during the first year of marriage." The patient had refused a previous offer of marriage because she would have to live with in-laws and then found herself living with a hypercritical sister-in-law, to whom she could never "speak up." ("I acted as if nothing happened, but I felt that she owed me an apology, which she never gave.") In June, 1944, the husband was drafted, and the patient moved into her mother's home. They had never got along because the mother disapproved of the patient's smoking and interfered with her need to be "independent."

Two weeks before the onset of the paralysis the patient felt that her troubles would soon be over. Her husband had been discharged from military service, and the patient looked forward to being in her own home. A week before the onset of the illness the patient was given the responsibility of running the home while her mother was vacationing. The patient did a meticulous housecleaning job, feeling that soon she would be free to do as she pleased. A week later (Sept. 7) she was stricken with extensive, severe paralytic poliomyelitis and was in a respirator.

CASE 11.—*Nurse (sister of Patient 10); age 23.*

The patient could "never gossip or bawl anyone out." She was the youngest of three children. The brother was the parents' favorite because of his scholastic and later successes. In 1941 she (like her sister, Case 10) failed in college chemistry. As her father was a chemical engineer, the patient felt she had not pleased him and was determined to make good in nurses' training, which she entered in 1943. Her goal was to become either a missionary nurse or an orthopedic nurse because she had heard that these specialities required a "lot of patience." The patient was a large, heavy young woman, who had weighed 200 lb. (90.7 kg.) at the age of 16 and was very much ashamed of her obesity. She had broken off with an only boy friend in 1943 because, in her opinion, she "didn't have anything to offer him."

When her sister became ill with poliomyelitis on Sept. 7, the patient was working on night duty as an affiliate nurse on a busy pediatric service and nursed her sister during the day. She recalled, "It was very hard work, like a rat race. I tried not to keep anyone waiting. I was there the week I took sick." The patient had continued working in the pediatric ward while febrile and with a severe headache, from September 16 until she was hospitalized, on September 23, when paralysis of the legs, arms, abdomen, and diaphragm developed.

CASE 12.—*Office worker and housewife; age 30.*

The patient described herself as "a very conscientious person" who "was doing a lot" before she became ill. She has been taking care of her two small children (2 and 3 years of age), as well as working overtime in an office. The patient said, "I just kept going so I wouldn't have any time to think." "The boss was a considerate person who left it up to us. I kept going and did more work than if he had kept after me." The patient disliked arguing, saying, "I would rather give in." She was a meticulous person and had always been "fast and quick." In June, 1940 at the age of 23), she married a self-centered man, to whom she "devoted" her life, "hoping to

make a go of their marriage." In June, 1944, her fourth child died 16 days post partum, and a month later the husband deserted her, leaving town with another woman. The patient had to find a job where she tried to forget by plunging into work "in order not to think" of her troubles. When her husband was drafted, in 1945, the patient became optimistic, hoping that the separation from the other woman would bring him home. The patient, who had been uncomfortable living with her mother-in-law, then planned to move into her own apartment. She moved on July 9, thinking that her troubles were over, and two days later severe, extensive poliomyelitis developed. Her husband, however, had taken offense because the patient had refused to help release him from military service and had never been interested in her since. The patient now says, "I shouldn't have given into him so much. I always tried to please everybody so as to have peace."

CASE 13.—*School girl; age 16.*

The patient stated that she was not "the worrying kind." Her feelings were "easily hurt" when she was criticized. On May 19 she had a tonsillectomy and was not disturbed by the experience or the sequelae. There was no undue concern about passing her ninth-grade examinations, on June 9, 1947. She was not particularly tired and enjoyed working in the garden and helping with the cooking. On June 15, she was "excited" about her father's birthday party, which was to be a surprise. She recalled, "It was the first big party we ever gave for Daddy. It was real excitement for me. I was worried if anyone would tell the secret." However, all went well, and the party was a great success. Five days later, on June 20, the patient became ill with severe, extensive poliomyelitis, requiring a respirator.

The factors of overconscientious striving and fatigue, which were present in the previous patients, were lacking in this patient. The effect of the tonsillectomy becomes significant, in keeping with the experiences reported by Aycock [2] and Francis.[3]

CASE 14.—*School girl; age 15.*

The patient was a very conscientious student and "wanted to be the valedictorian in the ninth grade." She had been at the head of her class from the fifth to the eighth grade and had been competing for first honors with her "best girl friend." The patient recalled that she "hardly ever went out nights. I worked hard. I never made an average of less than A in any subject."

In February, 1946, she won the health contest and was entered in a county-wide competition. She had "set her heart" on being the healthiest girl in the county and won the contest in May. She felt that her "troubles were over" for the year, but she was concerned about the talk of poliomyelitis in the vicinity. Two months before her illness, one case, that of a patient residing 20 miles away, had been reported, and a month before two other cases were present in the vicinity. The patient had been kept away from group activities and swimming, but she rode her bicycle more and had more time for tennis. On Aug. 26 she registered for the ninth grade, the last lap of the scholastic race. During the previous week she had waxed all the floors and ironed her brother's and her own clothes before leaving for camp (the prize for winning the health contest). She therefore did not have time to buy all her books for the coming term. For the first time she was concerned that she had overlooked something that was expected of her. The next day (Aug. 27) she experienced a headache and backache. At camp she participated in a strenuous athletic program (hikes, group games, and gymnastics). On Aug. 30 she went swimming and almost drowned, but did not call for help. She explained this inability to ask for assistance in an emergency by saying, "I never liked people to go out of their way for me."

On Aug. 31 she was driven home "almost across the state of Alabama and arrived exhausted and ill. Nevertheless she rode her bicycle to visit her girl friends, returning to clean up the house and wash the dishes. (She had started doing the house chores at the age of 9 and had voluntarily added new duties each year.) On the following day (Sept. 1), while visiting her 6-year-old sister and 2-year-old nephew, both of whom had been hospitalized for poliomyelitis on Aug. 31 (they later recovered without paralytic sequelae), the patient collapsed and 24 hours later (Sept. 2) had to be put in a respirator.

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2. Aycock, W. L.: Tonsillectomy and Poliomyelitis: Epidemiologic Considerations, Medicine **21**:65 (Feb.) 1942.

3. Francis, T., Jr.; Krill, C. E.; Toomey, J. A., and Mack, W. N.: Poliomyelitis Following Tonsillectomy in 5 Members of a Family: Epidemiologic Study, J. A. M. A. **119**:1392 (Aug. 22) 1942.

COMMENT

What can be the significance of these observations? Do the personality characteristics noted have some bearing on the severity and extent of the paralysis?

First, it must be emphasized that the series is small and that much further work is needed before the generality of the findings can be asserted with assurance. Nevertheless, the consistency of the findings in the series available for study warrants a preliminary report.

One feature of these cases—the extreme physical exertion preceding the acute illness—corroborates what many clinicians have observed in regard to the importance of fatigue. Isolated examples of extensive paralysis following "an unusually hard-fought football game" or "a rigorous mountain climb" have been reported, and there have been cases of paralytic illnesses associated with summer-camp athletic programs.[4]

In a study of 44 patients convalescent from poliomyelitis, Russell[5] found that "the amount of physical activity in the two days preceding the preparalytic phase did not influence the severity of the paralysis to a degree that was significant. After the onset of the meningitic symptoms, however, the continuation of physical activity, whether normal or excessive, had a highly significant correlation with the severity of the paralysis." Albrecht and Locke[6] have reported similar conclusions.

It is suggested that the case studies presented here throw light upon the kind of person who "overexerts" and the attitudes which prompt these exertions. There is disclosed a kind of person who is motivated by a basic anxiety to be accepted and to "overdo in order to gain acceptance." He is outwardly happy and healthy, enjoys physical activity, and is completely unaware of this fundamental personality need. His self-satisfaction is based upon the conviction that he is an independent person who asks no favors of anyone, never realizing that he is unable to do so. The average degree of spontaneous, aggressive self-assertion is replaced by a compulsive need to please in an overly conscientious, strenuous manner. When a difficult situation arises, the patient, who already is doing his very best, and at the same time is very concerned about possible failure, has to exert himself to the limit. This compulsive disposition may deprive such a person of the safeguard normally provided by a sense of fatigue, which would in the ordinary person prevent such extreme exertion.

The factor fatigue is only one of the several factors which may contribute to the "breaking down" of the protective mechanism. Thus, in Case 13, the patient had not been exercising but had had a tonsillectomy a month previously. The effect of this surgical procedure is now well recognized.[7] In Case 5 the patient was prevented from participating in athletics because of functional cardiac complaints, but he was repeatedly frustrated in school, had just entered a new school, where he would be able to get more sympathetic help, and was working "extra hard" at his studies.

4. Levinson, S. O.; Milzer, A., and Lewin, P.: Effect of Fatigue, Chilling and Mechanical Trauma on Resistance to Experimental Poliomyelitis, Am. J. Hyg. **42**:204 (Sept.) 1945.

5. Russell, W. R.: Poliomyelitis: The Pre-Paralytic Stage, and the Effect of Physical Activity on the Severity of the Paralysis, Brit. M. J. **2**:1023 (Dec. 27) 1947.

6. Albrecht, R. M., and Locke, F. B.: Effect of Physical Activity on Prognoses of Poliomyelitis, J. A. M. A. **146**:769 (June 30) 1951.

7. Aycock,[2] Francis, Krill, Toomey and Mack.[3]

SUMMARY

The personalities and life situations of 14 patients (5 males and 9 females), ranging in age from 14 to 35 years, with extensive severe paralytic poliomyelitis are described. There emerges from this small series a pattern of a fixed compulsive behavior. This type of maladaptive, rigid personality development is to be differentiated from the "nervous tension" of average persons under emotional stress, as well as from overt neurotic behavior. These patients appear to be happier, better adjusted, physically healthier, and more active than the average person, but they lack spontaneous, aggressive self-assertion; they have difficulty in criticizing others and do not experience anger. They are overly conscientious, anxious to be accepted, appease others, and at the same time are striving to be independent.

Frustrations are met by becoming more self-effacing, by adding to already heavy work loads, or by exercising excessively until there develops a pathological state of fatigue.

It would seem likely that patients with this type of compulsive behavior would continue to exert themselves during the preparalytic phase of poliomyelitis. There is adequate evidence available that the continuation of physical activity after the onset of meningitic symptoms has a highly significant correlation with the severity of the paralysis.

ANXIETY AND DEPRESSIVE STATES TREATED WITH ISONICOTINYL HYDRAZIDE (ISONIAZID)

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NEW AND more effective means of chemotherapy for mental disorders are constantly being sought by psychiatrists. The advent of mechanotherapy, such as electric shock therapy, has stimulated rather than deterred this search. With this in mind, it was noted that elevation of mood and euphoria were reported in the literature [1] as side-effects when patients with tuberculosis were treated with isoniazid. Accordingly, plans were made to study the effect of this drug on a group of depressed but nontuberculous patients seen in private psychiatric practice.

Actually, isoniazid is not new, having been synthesized in 1912,[2] but its recognized success against tuberculosis has been of but two years' duration. In addition to being a potent tuberculostatic agent, recently it has been used with increasing frequency in conditions other than pulmonary disease.

However, only a few reports have appeared on the use of isoniazid in the field of psychiatry. One of the earliest papers was that of Krieser, Sanderson, Vik, and Myers,[3] dealing primarily with schizophrenia, and with only one case of manic-depressive psychosis. Later MacKinnon, Michael, and Polatin [4] studied another group of schizophrenic patients.

Semicarbazide, closely related to isoniazid structurally, has been reported by Pfeiffer and associates [5] as being helpful in the therapy of resistant schizophrenic states.

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Oral isoniazid was supplied as I. N. H. through the courtesy of Eli Lilly & Company, Indianapolis, and injectable isoniazid as Nydrazid, through the courtesy of E. R. Squibb & Sons, New York.

1. Robitzek, E. H.; Selikoff, I. J., and Ornstein, G. G.: Chemotherapy of Human Tuberculosis with Hydrazine Derivatives of Isonicotinic Acid (Preliminary Report of Representative Cases), Quart. Bull. Sea View Hosp. **8**:27 (Jan.) 1952.

2. Meyer, H., and Mally, J.: Hydrazine Derivatives of Pyridinecarboxylic Acids, Monatsschr. Psychiat. u. Neurol. **33**:400, 1912.

3. Krieser, A. E.; Sanderson, A. G.; Vik, M., and Myers, J. A.: Effects of Isonicotinic Acid Hydrazide in Mentally Ill Patients, Dis. Chest **23**:28 (Jan.) 1953.

4. MacKinnon, I. H.; Michael, S., and Polatin, P.: The Effects of Isonicotinic Acid Hydrazide on Schizophrenic Patients, read before The American Psychiatric Association, Los Angeles, May 8, 1953.

5. Reilly, R. W., and others: Therapy of Resistant Schizophrenia with Semicarbazide and Photic Stimulation, Federation Proc **12**:359 (March) 1953.

As far as can be ascertained, the present study is the first in which isoniazid has been employed in the treatment of anxiety states and psychoneurotic, agitated, and manic-depressive depressions.

MATERIALS AND METHODS

Material.—This report deals with the early results noted in a group of 41 patients, most of whom were suffering from depressive states of the psychoneurotic, agitated, or manic-depressive types, and one of whom had a pure anxiety state. They were given isoniazid, and the effect on their mental status, as well as on their various symptoms, was studied.

Women predominated, in a ratio of 3.5:1, there being 32 women and 9 men in the series. Their ages ranged from 26 to 76, but most of them were under 50. From a diagnostic standpoint, there were 11 cases of manic-depressive depression, 17 cases of psychoneurotic depression, 12 cases of agitated depressions, and 1 case of pure anxiety state.

Twenty-two patients gave a history of one or more previous depressions; in addition, 3 were considered to have had chronic depressions, of five to six years' duration. Of the 22 patients, 15 formerly had required electric shock therapy. The three patients with chronic depression, as well as four other patients, received electric shock therapy during their present episode, but prior to being placed on treatment with isoniazid.

The majority of our patients had also received a combination of sedatives, amphetamines, and diphenylhydantoin, as well as hormones, desoxycorticosterone, and vitamins, for both their present and their past episodes. The efficacy of such therapy alone was minimal and usually produced no improvement. It was only for some of the most recently treated patients of our series that the use of amphetamines and diphenylhydantoin was omitted and therapy with isoniazid was begun after the initial examination.

Procedure.—After a complete neurological examination and psychiatric evaluation the patient was placed under treatment with 50 mg. of isoniazid, given orally three times a day. After one week, if no side-effects were noted, the dose was increased to 100 mg. three times a day. In a few instances the dose was further increased to the limit of tolerance, but most patients were held at this point, which amounted to less than 5 mg. per kilogram of body weight—the level beyond which observers have reported undesirable side-effects. Some of the more recent patients were started immediately on treatment with 100 mg. three times a day. The drug was administered one hour after meals. To one patient (Case 37), who failed to respond after one month on this regimen, 100 mg. of isoniazid was given three times a day parenterally instead of orally.

Administration of the drug was continued for several weeks after the symptoms of depression had disappeared. In some cases the drug was abruptly discontinued, often by the patient himself, but in most instances the dose was tapered off over a period of two or more weeks, depending on the patient's response. Tapering off the drug was not regarded as essential, but was considered preferable to abrupt termination.

REPORT OF CASES

Seven patients were chosen from our series as representative of the various types treated.

CASE 1.—A. B., a woman aged 27, was first seen on Sept. 13, 1952. Since May, 1951, she had had intermittent nocturnal attacks of cramps in the lower abdomen followed by vomiting—the symptoms recurring every few months. The attacks became more frequent in the summer of 1952, when she became emotionally upset because her husband had a convulsion which heralded the recurrence of a cerebral tumor. Her insecurity and anxiety symptoms were intensified a few months later, when her only brother was inducted into the Army. It was in this setting, while feeling deserted and rejected, that she sought treatment. In addition to the abdominal pain and vomiting, she complained of feelings of tension, tremulousness, loss of appetite, and considerable loss of weight. Although she had always been considerably underweight, she weighed only 84 lb. (38.1 kg.) when first examined. A diagnosis of psychoneurotic anxiety and malnutrition was made. Treatment consisted of psychotherapy, sedatives, and vitamins.

By Nov. 4 there had been essentially no improvement, and she was then given isoniazid, 50 mg. three times a day. Definite improvement was noted during the next three weeks. On Nov. 27 she contracted influenza, complicated by sinusitis, which required a course of treatment with several antibiotics. Because of this, the patient discontinued the isoniazid. When next seen, on Dec. 30, the abdominal pain and vomiting had recurred; she felt both weak and tenser and her weight had dropped. Isoniazid, 50 mg. three times a day, and vitamins were again prescribed.

By Jan. 27, 1953, she felt exceptionally well. She felt more secure, and no longer tense; the gastric complaints had not recurred, and the tremulousness had disappeared. The appetite was described as "terrific," and she had gained 5 lb. (2.3 kg.). The same dose of isoniazid was continued, along with the vitamins. Continued improvement was noted on her subsequent visits, and on April 7 her weight reached 92 lb. (42.2 kg.). All her subjective anxiety and associated somatic symptoms had disappeared.

CASE 3.—A. C., a man aged 66, was first seen in 1947, when he was 60 years old, because of a depression of several months' duration. He was restless and complained of insomnia, inability to concentrate, and loss of libido. He was given 19 electric shock treatments, with improvement, but he never felt completely well. Since 1947 he had been seen approximately once a month, but had remained restless and unable to sleep unless he took small doses of barbiturates. He had received hormones and vitamins, with indifferent results, and his symptoms remained essentially unchanged.

Because the condition was one of chronic depression not severe enough to warrant further shock therapy, he was placed on treatment with isoniazid, 100 mg. three times a day on Jan. 8, 1953. When he was seen on Feb. 17, the appetite had improved; he was sleeping better and felt stronger. The urine showed a trace of sugar, but none was found on subsequent tests. On March 31 his improvement had continued and he showed no signs of depression.

CASE 18.—W. R., a man aged 65, was examined in the hospital on Oct. 4, 1952, because of anorexia, lack of interest, suicidal thinking, and wringing of the hands. A diagnosis of agitated depression was made. He had received electric shock therapy in 1950 for a previous depression. It was thought best to temporize on this admission because he had sustained a hip fracture in 1951 as the result of a fall. Therefore amphetamines, barbiturates, desoxycorticosterone, and vitamins were liberally administered from Oct. 4 to Oct. 21, 1952, without improvement.

On Oct. 21 he was placed on isoniazid therapy, 50 mg. four times a day, but no change was noted. On Oct. 25 the dose of isoniazid dose was increased to 100 mg. three times a day, and four days later he showed marked improvement, being able to leave the hospital on Nov. 1. He returned to work but continued to take amphetamines, sedatives, vitamins, and 100 mg. of isoniazid three times a day. All these medicaments except the isoniazid were discontinued in the middle of March, 1953. The isoniazid therapy was discontinued gradually during the early part of April. When interviewed on April 23, he was in good spirits, and the appetite was excellent.

CASE 26.—R. M., a woman aged 71, was seen first in July, 1945. In 1932, at the age of 50, she had had a depression and would not talk or eat voluntarily for two months. In July, 1945, at the age of 63, she had smothering spells, dizziness, insomnia, mental slowing, and depression. She was given six electric shock treatments, with recovery. The depression recurred in March, 1946, and again she was given six shock treatments, with recovery, but after a relapse in June, 1946, she had to have six additional treatments. Six more treatments were required for another depressive episode in April, 1948. Relapses in December, 1948, and August, 1949, necessitated 10 and 7 shock treatments, respectively.

In February, 1953, when she was disinterested, depressed, not eating, and unable to sleep, she received two more shock treatments, without improvement. After the second treatment, on Friday, Feb. 13, she experienced severe pain in the right knee and could not walk for two weeks. X-ray studies revealed calcification of the popliteal vessels, and it was felt inadvisable to continue electric shock therapy. Therefore, on Feb. 16, isoniazid, 100 mg., was given twice a day, after breakfast and after lunch. By April 16 she had improved generally; she was interested, up and about, and no longer depressed, and the appetite was good. On April 29

she was better than she had been in a long time, was interested in her garden and had gained several pounds. Isoniazid was continued in a dose of 100 mg. twice a day, with continued improvement.

CASE 32.—B. B., a woman aged 27, was first seen on Jan. 19, 1947, because of anxiety symptoms consisting of fears, insomnia, and agitation centered on her marital maladjustment. There were mild symptoms of depression, consisting of a feeling of insecurity and occasional thoughts of suicide. She received intensive psychotherapy, supplemented by bromides over a period of one and one-half years. During this 18-month period the symptoms and general adjustment improved.

She was next seen on July 18, 1952, at the age of 32, complaining of severe agitation combined with a strong feeling of depression and extreme psychomotor retardation. She was confused, and unable to make a decision, showed poor judgment, and again was quarreling with her husband. Insomnia, anorexia, and loss of weight were also present. She was hospitalized and received 11 electric shock treatments and subcoma insulin therapy, followed by intensive psychotherapy, with sessions five or six times a week at first. All the symptoms improved, and she was discharged; but, despite good intentions, she was unable to return to work or even to do housework adequately. Psychotherapy was continued, but in August, 1952, she again became more depressed, felt hopeless, lost her self-confidence, and her marital adjustment became worse. Again, she showed psychomotor retardation, lost interest in any type of activity, and cried frequently. During this time barbiturates, amphetamines, vitamins, and hormones were given, without appreciable change.

She became progressively more depressed in October, 1952, and on Oct. 31, while complaining of inability to concentrate, loss of interest and procrastination, she was placed on isoniazid treatment, in a dose of 50 mg. three times a day. There was essentially no change the following week, and the dose was increased to 100 mg. three times a day. On Nov. 13, she was smiling and showed more animation. She felt less depressed and began to speak of the possibility of resuming her old job. On Dec. 18 she was greatly improved and showed normal psychomotor activity. She had regained interest in her former social activities and reported that her husband had seen a great improvement. When seen three weeks later, she reported having been active socially over the holiday season. She had been irregular in her medication, but usually took the drug once or twice a day. She was not feeling so well generally and seemed to be mildly "let down." Isoniazid, 100 mg. three times a day, was prescribed. When seen two weeks later, on Jan. 29, 1953, she was again feeling better and showed no signs of depression. She reported being busy and feeling much closer to her husband. Isoniazid was reduced to 100 mg. twice a day. Improvement continued, and on Feb. 12 the dose was further reduced to 50 mg. twice a day. On March 19 the medication was discontinued entirely and the patient was happy, smiling, and asymptomatic. She was seen again on April 16, at which time she was feeling well and had no complaints.

CASE 37.—F. M., a woman aged 39, was first seen on March 20, 1952, because of agitation, confusion, and bewilderment. She had been depressed for six months and had received 12 electric shock treatments about one month previously, without any improvement. She complained of insomnia, anorexia, lack of self-confidence, and inability to manage her home. Treatment consisted of supportive psychotherapy, a total-push program on the part of her family and friends, and administration of sedatives, vasodilators, and vitamins. It was necessary to keep her away from home until September, 1952, so that someone else could care for her. At that time her symptoms were greatly improved, and by mid-October, 1952, she was essentially asymptomatic.

When seen on Feb. 27, 1953, she had been depressed for five days and again was showing psychomotor retardation. She complained of having no energy and of feeling "dopey." There had been a 5 lb. (2.3 kg.) loss of weight in five days. She was placed on treatment with 50 mg. of isoniazid three times a day and barbiturates. One week later the symptoms were worse, and the isoniazid was increased to 100 mg. three times a day. On March 12 there was no improvement, and by March 19 she was agitated, restless, and unable to manager her domestic responsibilities. Insomnia was present, and the weight had dropped 3 lb. (1.3 kg.). She was hospitalized on March 23 and the same medication was maintained, plus daily psychotherapeutic interviews. The depression became steadily severer and on March 27 oral use of isoniazid was discontinued and parenteral administration of 100 mg. of isoniazid three times a day was sub-

stituted. Three days later signs of improvement, especially in psychomotor activity, were noted. Gradually over the next five weeks, she became less depressed; mentation cleared, and the appetite improved. On April 27 oral administration of 100 mg. of isoniazid was substituted for one injection, and on May 2 another 100-mg. tablet was substituted for the second injection. After this change no interference with her continued improvement was noted.

CASE 38.—E. M., a woman aged 41, was first seen in September, 1950, because of anxiety symptoms and feelings of exhaustion. The condition gradually improved on psychotherapy, supplemented by mild sedatives, but in July, 1951, she became tenser and more agitated over the impending marriage of her daughter. At that time there was a suggestion of mild depression. During the next eight months, on the same regimen, the symptoms improved.

She was next seen on Feb. 23, 1953, at which time she complained of agitation and depression of six weeks' duration. Insomnia, anorexia, and loss of weight were present. She showed evidence of marked psychomotor retardation, and all the symptoms were severer than on any previous occasion. She was placed on a regimen of 50 mg. of isoniazid three times a day and phenobarbital in the afternoon and evening. One week later she reported having had several days on which she felt better. The isoniazid was increased to 100 mg. three times a day. During the next three weeks there was a steady improvement in all her symptoms. However, on each of her next two weekly visits she felt worse, and all her complaints became severer. It then developed that during these two weeks she had been highly irregular in taking the isoniazid, often omitting it altogether or taking only one tablet a day. On April 11 the original program

TABLE 1.—*Improvement According to Symptoms*

Symptoms	No. of Patients	No. Improved	Percentage Improved
Depressed mood	40	28	70.0
Psychomotor retardation	41	30	73.2
Insomnia	25	22	88.0
Anorexia	33	24	72.7
Loss of weight	27	20	74.1
Agitation	31	22	71.0
Crying	18	12	66.7
Somatic complaints	37	23	62.2

of medication was again prescribed; and when she returned the following week, there was subjective and objective improvement in all symptoms. On April 23 the patient reported having had two unusually good days. She was sleeping well; the appetite had improved, and there had been a 3 lb. gain in weight. She was instructed to continue taking the isoniazid three times a day.

RESULTS

All the patients in this study were followed for at least one month, and some for as long as six months, the average period being about three months. Table 1 shows the percentage of cases in which a given symptom improved under treatment with isoniazid. The results are in contrast in some instances with the total evaluation of the patient, since many of the patients rated as failures on isoniazid therapy actually showed improvement in one or more of their presenting symptoms. This would indicate that isoniazid is of value in treating such specific symptoms as insomnia and, to a less degree, anorexia and loss of weight in some instances in which elevation of the mood could not be produced.

Of the 41 patients treated with isoniazid in this series, 28, or 68.3%, were rated as improved. This compares with an incidence of 77.3% who had required electric shock therapy for their former episodes. Furthermore, 13 patients out of 22 who formerly had required electric shock therapy improved on isoniazid alone. Lending credence to this finding is the fact that half these 13 patients were in the series treated independently by each of us.

Of the 13 patients who failed to respond to isoniazid, 5 also failed to respond to subsequent electric shock therapy, and another discontinued treatment after reporting improvement for the first time since his illness began.

Table 2 shows the percentage of improvement that occurred in each of the diagnostic subgroups. There was no significant difference between the number improved in any subgroup and the over-all improvement rate, of 68.3%. Table 3 presents an analysis of improvement rates for the various age groups. The number of patients included in each subgroup is too small to permit one to draw any conclusions. However, the Table is included because of its interesting implications regarding the therapeutic value of isoniazid in the younger age groups.

TOXICITY AND SIDE-EFFECTS

In this series of 41 patients there have been no serious side-effects or toxic reactions. Although reported as producing reducing substances in the urine,[6] isoniazid

TABLE 2.—*Improvement According to Diagnoses*

Diagnosis	No. of Patients	No. Improved	Percentage Improved
Agitated depression	12	8	66.7
Psychoneurotic depression	17	11	64.7
Manic-depressive depression	11	8	72.7
Pure anxiety state	1	1	....
Total	41	28	68.3

TABLE 3.—*Improvement According to Age*

Age	No. of Patients	No. Improved	Percentage Improved
26-29	3	2	66.7
30-39	9	9	100.0
40-49	9	7	77.8
50-59	6	3	50.0
60-69	10	5	50.0
70-76	4	2	50.0

has been given to two diabetic patients and the urine has remained sugar-free. In another diabetic treated with isoniazid too recently to be included in the series a dark substance precipitated in the test for sugar. In Case 3, on one occasion there was a trace of sugar, but on subsequent examinations the urine was negative.

Six patients with tuberculosis combined with diabetes who are under treatment at Hamilton County Dunham Tuberculosis Hospital have had no increase in the severity of the diabetes while under treatment with isoniazid.[7]

In some of our patients hyperreflexia developed, but the appearance of this sign was not considered sufficient reason for stopping use of the drug or reducing the dose.

One patient, not included in this series because she was on isoniazid therapy only two days, reported that the drug had a "thyroid-like" effect. In the past this patient could not tolerate thyroid therapy or any stimulants.

6. Elmendorf, D. F., Jr., and others: Absorption, Distribution, Excretion, and Short-Term Toxicity of Isonicotinic Acid Hydrazid (Nydrazid) in Man, Am. Rev. Tuberc. **65**:429 (April) 1952.

7. Nimitz, H.: Personal communication to the authors.

Hunter [8] has reported a psychosis following administration of isoniazid in doses of 8 to 10 mg. per kilogram of body weight for one month. This Korsakoff-like psychosis persisted for two months after isoniazid was discontinued. In our series there was no such complication, but no patient received more than 5 mg. per kilogram.

COMMENT

It should be noted that in selecting the patients for this series, the patients with the severest depressions were omitted, as they required immediate hospitalization and electric shock therapy. For the same reason, the patients who were considered suicidal were also omitted.

Evaluation of treatment in a group of patients with anxiety and depression presents numerous problems which make simple clinical interpretation difficult. For example, there are a large number of uncontrollable variables, such as ordinary remissions and exacerbations. In addition, one must raise such questions as the effect that any drug or placebo administered might have, the effect of psychotherapy, and the probable duration of illness without treatment.

Most of our patients had received psychotherapy supplemented with amphetamines and sedatives for one to several months before treatment with isoniazid was begun. This regimen alone failed to produce improvement. Furthermore, the patients receiving amphetamines before isoniazid not only did not recover more quickly, but actually their improvement was delayed by the length of time they waited before isoniazid was administered. About half the patients received amphetamines along with the isoniazid, but no significant difference in their rate of improvement was noted. The failure of intensive psychotherapy alone, even when supplemented with amphetamines and barbiturates, and the subsequent recovery when psychotherapy was combined with isoniazid is strikingly demonstrated in Case *32*.

Some improvement was usually noticed in from one to three weeks after administration of the drug, a rate which is appreciably faster than the rate of improvement occurring in the course of a normal remission.

Some patients who had improved on full doses of isoniazid subsequently became worse when the dose was reduced prematurely. They quickly improved again when the former dose was resumed, as seen in Cases *32* and *38*, indicating that isoniazid was the major factor in producing the improvement. The improvement in Case *37* when isoniazid was given parenterally after no improvement had occurred with oral administration suggests that the parenteral route should be tried if the oral route fails to help.

Patients with chronic depression seemed to improve particularly well, whereas patients with numerous associated organic disorders, such as heart trouble, diabetes, postencephalitic tremor, and senile skin changes, failed to improve.

Our figure of 68.3% improvement contrasts sharply with the report of Krieser and associates [3] of 37.5% improvement. However, their group consisted largely of schizophrenic patients. One patient in two previous depressions had required seven shock treatments. On the present occasion, when isoniazid was used, he improved with only two treatments. Two other patients treated too recently with

8. Hunter, R. A.: Confusional Psychosis with Residual Organic Cerebral Impairment Following Isoniazid Treatment, Lancet **2**:960 (Nov. 15) 1952.

isoniazid to be included in this series likewise have improved with fewer shock treatments than the number required during previous depressions. One wonders, therefore, whether isoniazid used in conjunction with shock therapy might shorten the number of treatments necessary.

SUMMARY AND CONCLUSIONS

Of 41 patients suffering from anxiety or depressions of the agitated, psychoneurotic, or manic-depressive types, 28, or 68.3%, improved after receiving isoniazid.

Of the 21 patients who had required electric shock therapy for previous episodes, 13, or 59.1%, improved on isoniazid alone.

Of the 13 patients considered failures, 5 failed to show improvement even after receiving subsequent electric shock therapy.

Some improvement was usually noted within three weeks if the patient was going to respond.

If oral administration of isoniazid fails to produce improvement, the parenteral route should be tried.

Isoniazid can be administered safely to diabetic patients.

Isoniazid used in conjunction with electric shock therapy may reduce the number of treatments necessary.

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CEREBROSPINAL NEMATODIASIS

Focal Encephalomyelomalacia of Animals Caused by Nematodes (Setaria Digitata); A Disease Which May Occur in Man

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OBSERVATIONS on diseases of domesticated animals often have a lengthy incubation period before they are noticed by medical workers; inaccessibility of veterinary journals plays some part, while factual relevance to medical problems may not be quickly evident. Many examples could be given in which, indeed, studies in animal pathology were the start of a train of events leading to the ultimate identification of comparable disorders or focused attention on "new" etiological factors in the production of disease. A classic instance is the observation of Griffith Evans [1] (1880) that a trypanosome (Trypanosoma evansi) caused surra (trypanosomiasis) in mules and horses in India. This must have had far-reaching effects, for it surely had an influence on the work of Bruce, Dutton, and Castellani (Scott,[2] 1942) on the cause of African sleeping sickness (trypanosomiasis) in animals and man, more than 20 years later.

The present studies on cerebrospinal nematodiasis may once more stress the potential medical value of studies on animal disease. There is evidence that the role of nematodes in the production of neurological disorders in animals may be a global problem. This is particularly perspicuous if one considers, along with the neural nematodiasis, the subject of helminthic ocular disease in animals and man. We believe there may be a helminthic neuro-ocular complex, bound up with the migratory paths taken by the worms in their wandering through tissue to reach their final anatomical resting place, which may be either the eye or the central nervous system.

The disease now called cerebrospinal nematodiasis has occurred in domesticated animals in the Far East for more than 30 years and was once widely known as "lumbar paralysis." There is inferential evidence that the same neuroparalysis has

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Formerly at the Southwest Foundation for Research and Education; at present at Medical Laboratories, Army Chemical Center, Edgewood, Md. (Dr. Innes).

1. Evans, G.: Surra Disease in the Dera Ismail Khan District, Report No. 7, Punjab Military Department, 1880.

2. Scott, H. H.: History of Tropical Medicine, Ed. 2, Baltimore, Williams & Wilkins Company, 1942, Vol. 2, p. 453.

existed in many other parts of the world in various species but, for lack of careful pathological study, has not been clearly defined. In particular, we refer to so-called kumri (lumbar paralysis) of horses in India, Burma, and Assam, for this condition was described clinically in veterinary writings of more than a century ago, while even the idea of a probable causal association with worms (filariae) goes back many years (Railliet,[3] 1895; Macalister,[4] 1917).

It should be stressed that this neuroparalysis in Japan, Korea, and Ceylon is not a rare disorder, i. e., one in which helminths on unique occasions accidentally wander into the central nervous system. If Japanese encephalitis B of man deserves the designation epidemic, then the adjective epizootic for the cerebrospinal nematodiasis of animals is justified. In some areas in Japan, and in some years, the disease has been rife, affecting, for example, about 6% of sheep, although many animals apparently recovered, with or without residual neurological defects.

This paper presents a condensed account of many publications which have appeared elsewhere, mainly in veterinary journals (Niimi and Kimura,[5] 1939-1941; Yamagiwa and Shoho,[6] 1944; Tanaka and associates,[7] 1945; Shoho,[8] 1951; Innes, Shoho, and Pillai,[9] 1952, and Ishii and associates,[10] 1953), while a paper by Innes [11] (1951) dealt specifically with the caprine paralysis which occurred in Ceylon. Great credit for the contributions which led to the solution of the etiology of this strange nervous disorder must be given to Japanese workers, but many of their papers have been inaccessible because of the war and because they were published in Japanese. Much of the Japanese work has been published in a Special Korean Research Commission Report (1939-1943), in five volumes, but, unfortunately, in Japanese, and translations are unavailable. The Japanese who were largely concerned in various aspects of the work were Kimura, Niimi, and 29 others,[12] although there were others engaged in studies earlier or later than this.

3. Railliet, A. L. J.: Traité de zoologie médicale et agricole, Ed. 2, Paris, Asselin & Houzeau, 1895, p. 507.

4. Macalister, G. H. K.: Combined Diffuse Sclerosis and Central Poliomyelitis of Horses, Mem. Dept. Agric. India **2**:207, 1917.

5. Niimi, D., and Kimura, T.: Histological Changes in the Central Nervous System in Lumbar Paralysis of Sheep in Korea, Tr. Soc. path. jap. **29**:466, 1939; **30**:539, 1940; **31**:609, 1941.

6. Yamagiwa, S., and Shoho, C.: Zur Pathologie der Setariosis der Schäf: (Eine neurohistologische Studie), Jap. J. Vet. Sc. **6**:413, 1944.

7. Tanaka, T.; Suu, S.; Shoho, C., and Yamagiwa, S.: Beitrag zur Pathologie der Setariosis der Pferde: (Eine neurohistologische Studie), Jap J. Vet. Sc. **7**:117, 1945.

8. Shoho, C.: Pathology of Setariasis in Japan and Its Significance in Veterinary and Medical Science, Jap. J. Exper. Med. **21**:449, 1951.

9. Innes, J. R. M.; Shoho, C., and Pillai, C. P.: Epizootic Cerebro-Spinal Nematodiasis: Focal Encephalomyelomalacia in Animals in the Orient Caused by Immature Setaria Digitata, Brit. Vet. J. **108**:71, 1952.

10. Ishii, S.; Yajima, A.; Sugawa, Y.; Ishiwara, T.; Ogata, T., and Hashiguchi, Y.: Brit. Vet. J. **109**:160, 1953.

11. Innes, J. R. M.: Necrotising Encephalomyelitis of Unknown Etiology in Goats in Ceylon with Similarities to Setariasis of Sheep, Horses, and Goats in Japan, Brit. Vet. J. **107**:187, 1951.

12. There were three chief groups of workers: the first, in Korea (the Research Commission), mainly from the Pusan Serum Institute for Animal Diseases; the second from the National Institute of Epizootics, to which Dr. Ishii belonged, and the third, from the Institute for Infectious Diseases, in University of Tokyo, to which Dr. Yamagiwa, Dr. Shoho, and Dr. Tanaka belonged. The last two groups worked exclusively with the disease in Japan.

CLINICAL ASPECTS

All observations indicate that from the beginning the disease was recognized (in Japan, Korea, and Ceylon) as occurring annually in the late summer and autumn, i. e., at a period coinciding with, or following, the appearance of insect vectors. Until the cause and vectors were known, this seasonal feature was puzzling and was responsible for much conjecture regarding the etiology.

Young and adult animals are affected, but no cases of the disease have been clearly identified in newborn lambs, kids, or foals. (The probability of an associated process being the explanation of a condition of blindness and paralysis in newborn and young calves will be discussed elsewhere by one of us [C. S.].) The disease is thus totally unlike swayback, or inherited cerebellar ataxia, in newborn and young lambs, with which it may be confused superficially in some countries (Innes,[13] 1949; van Bogaert and Innes,[14] 1950). Affected animals show motor weakness and incoordination of all four limbs, or the hindlimbs alone, leading sometimes to complete posterior paralysis. The onset may be dramatically acute, the animal being apparently normal one day and found lying helpless the next. In other animals the course is more insidious and subacute, motor weakness gradually developing and causing them to sway and tumble when attempts are made to walk. Animals in the acute stage may die, although not necessarily of the nervous disease, in a few days, or they may linger on for a week or so. Animals with a less acute form may recover and thereafter show some (or no) residual neurological defects, such as a weakness of limbs and impaired, limping gait or a drooping eyelid or ear. The disease is usually unaccompanied with constitutional signs or fever. From a consideration of the pathology, the clinical variations seen in different cases, with diverse degrees of acuity, are understandable and may be related to the apparently haphazard anatomical location of the causal worm, and the lesion it produces, in the nervous system. Full data are not available on the cerebrospinal fluid. Because of the presence of meningeal infiltrations, it would be reasonable to expect pleocytosis in most cases, and many eosinophiles might be found if differential counts were made.

Other clinical aspects, such as multiple infections or reinfection in successive years, or even in the same season, are discussed later. In the field, because of the intrinsic difficulties associated with accurate diagnosis of nervous diseases in animals, cerebrospinal nematodiasis may be mistaken for other paralytic entities, particularly some of the viral encephalitides, in the countries where they occur.

PATHOLOGY

There are no fundamental differences in the nature of the typical acute nervous lesions in either the sheep, goats, and horses in Japan and Korea, on the one hand, or the goats in Ceylon, on the other. The disease process can thus be considered an entity, irrespective of the neuroanatomical location of the lesion, the species involved, or the country of origin of the animal.

13. Innes, J. R. M.: Demyelinating Diseases of Animals: Swayback; Demyelinating Disease of Lambs with Affinities to Schilder's Encephalitis; Role of Copper in Aetiology, A. Res. Nerv. & Ment. Dis., Proc. (1948) **28**:75, 1950.

14. van Bogaert, L., and Innes, J. R. M.: Cerebellar Disorders in Lambs: A Study in Animal Neuropathology with Some Comments on Ovine Neuroanatomy, Arch. Path. **50**:36, 1950.

In many cases only a single lesion is found; in some there may be two or three; in a few cases only are there more. Foci may be found anywhere in the central nervous system; thus, there is an apparently fortuitous localization of the worms once it reaches the craniovertebral canal, where the parasite shows a total disregard for neuroanatomical landmarks. Yet in Japan it has repeatedly been noted that the

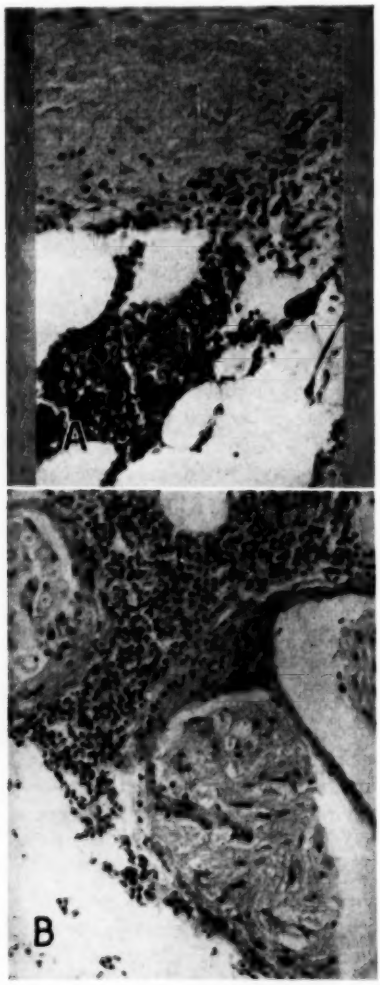

Fig. 1.—Spinal cord of a goat (Ceylon) with nematodiasis: *A*, cellular infiltration in epidural tissue; *B*, cellular infiltration around the ventral nerve roots, with many polymorphonuclear leucocytes. Hematoxylin-eosin stain; × 200.

spinal cord and the thalamus may be favored sites, but many other regions have been identified as loci of damage. This random distribution of foci correlates with the reported variety of clinical signs indicating motor weakness, ataxia, and paralysis of the forelimbs and/or hindlimbs and with the fact that some animals

may recover. Clearly, a lesion of the type to be described below, and located in the lower part of the cord, would not have such drastic effects as one at a higher level, in the brain stem. Furthermore, as the lesion is approximately of the same size in an affected animal, whether a sheep, goat, or horse, it might not produce as severe neurological signs in animals with such a large nervous system as that of the horse or man. Indeed, microscopic lesions have been found by Tanaka and associates [7] in the cerebral cortex of horses which showed no nervous symptoms during life.

Unless the lesion is hemorrhagic, and this may depend on the circumstance of the nematode striking a main vessel, accurate macroscopic detection of pathological change might be difficult. With hemorrhagic softening the task becomes easier. In the present study, it was, however, found necessary in some cases to embed the entire nervous system for section cutting. Coronal sections were thus made of the brains of several goats (from Ceylon) at every 4 to 5 mm. level, while transverse sections were alternated with longitudinal sections of the whole cord; after examination of representative sections, further preparations (even serial)

Fig. 2.—Spinal cord of sheep (Japan) with nematodiasis, showing cracks and crevices due to streaking liquefaction in the ventrolateral columns of the white matter. Hematoxylin-eosin stain; × 10.

were made of any tissue in which a lesion was suspected. The Japanese workers relied, in the first place, on macroscopic examination of transverse sections of the brain and cord 3 to 4 mm. in thickness.

Except for a solitary malacic lesion, or more than one, the entire nervous system is normal, and areas only a few millimeters away may reveal no structural damage except for the secondary degeneration, to be mentioned later. An important feature is thus the restricted, but irregular, boundaries of the focal malacia. Many lesions seem to have an obvious tracking inward from the pia, although this may be evident only when serial sections are studied. Cellular infiltrations in the meninges are constant but variable and may contain lymphocytes and polymorphonuclear leucocytes, while eosinophiles may vary in number but be prominent (Fig. 1). These infiltrations may involve epidural, subdural, and leptomeningeal tissue and spinal nerve roots in a patchy manner and may extend away from areas adjacent to the malacic focus, and there may be minute hemorrhages in the same

situations. Meningeal and radicular reactions may, consequently, be a guide in further search for a central focus if the latter is not found readily; but they may also be misleading, for after random selection of nerve tissue for sections they might lend support to the original idea that only a selective meningitis was present.

Sections taken from many serial levels near a true focus reveal the following features: Hemorrhage is variable and may be absent. Under the low-power lens, sections may have the appearance of cracks and crevices (Fig. 2), although some

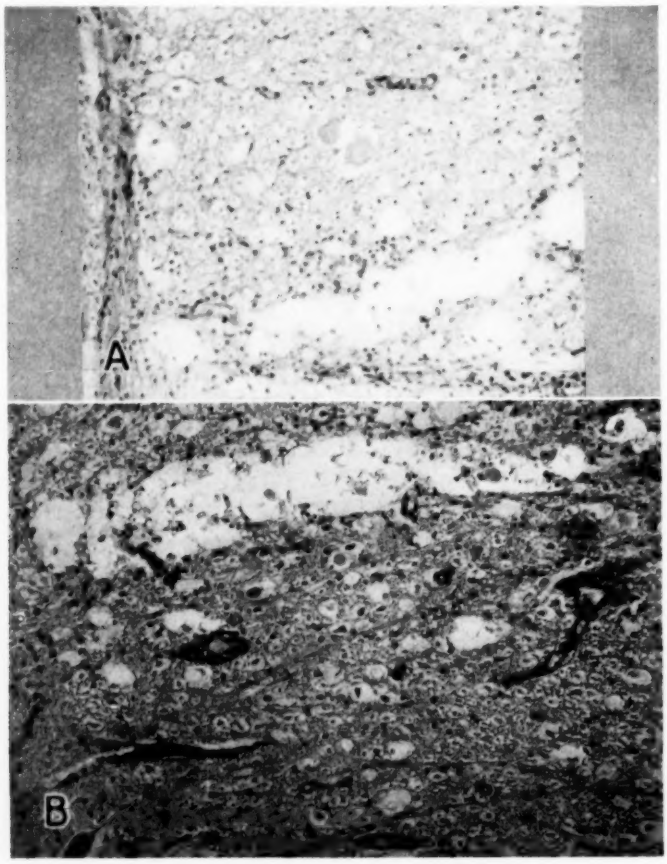

Fig. 3.—Nematodiasis in goats (Ceylon).

A, margin of lesion in cord, showing absence of pial infiltration, a straggling area of liquefaction and microcavitation, two grossly swollen axis-cylinders, and many large empty, ballooned "myelin" spaces. Hematoxylin-eosin stain; × 200.

B, section through the center of a focus involving the white matter and the edge of the gray matter, in a case other than that of *A*. Perivascular cuffing, microcavitation, and many swollen axis-cylinders appear. Hematoxylin-eosin stain; × 90.

of this may be exaggerated by a falling out of tissue. A fully developed lesion (and full development may require only a few days in the living animal) is one of acute softening, in which all structures disappear, leading to microcavitation

(Figs. 3 and 5). *Gemästete Glia* may be abundant in softened areas (Fig. 5*B*) or may be present also in the perivascular cuffs and sleeves, which in and around the lesion are formed by cellular infiltrations of lymphocytes, and eosinophiles may be numerous. A salient feature concerns the axis-cylinders. In areas in and adjacent to the malacic focus, but occasionally lying isolated in spaces produced by liquefaction of myelin, there are irregularly shaped, homogeneous (sometimes faintly granular), globose bodies, faintly stained with cytoplasmic stains, unstainable for lipids or myelin, showing an affinity for any of the metallic substances

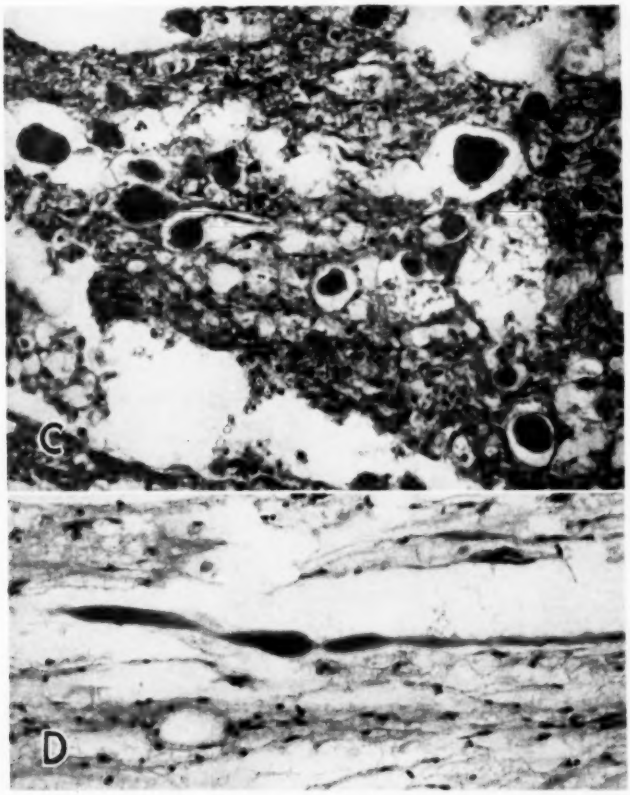

Fig. 3 (continued).—*C*, section through the center of a liquefied lesion from the same case as that of *A*, under high magnification, showing enormous swollen axis-cylinders in a malacic focus. Hematoxylin-eosin stain; × 400.

D, longitudinal section from the same case as that of *A* and *C*, demonstrating gross beading of a single axis-cylinder. Hematoxylin-eosin stain; × 200.

used in impregnation methods for axis-cylinders (or glia) (Figs. 3*C* and 5*B*). Some may be two to three times the diameter of normal axis-cylinders, but many are tremendously enlarged. All doubts that these are axis-cylinders disappear if longitudinal sections are examined (Fig. 3*D*), for all stages, from delicate to gross beading and complete fragmentation, can be seen. A bizarre collection of corkscrew spirals, glomerular balls, and collateral excrescences of axis-cylinders may

be found in one field. Further, if a series of sections are made above and below the malacic focus, axis-cylinder swellings can be traced in an ascending and a descending direction and can be correlated with the primary focus. At levels a few millimeters from the area of malacia, this secondary degeneration may be the only histological damage (Fig. 6*D* and *E*) and may be a clue of some value in the search for the true pathological softening.

Serial sections reveal that a malacic focus may be small in its transverse diameter but tortuous in its extension in any direction, and in the cord this may be an obliquely longitudinal one. The focus may, however, involve most of the white matter on one side of the cord only, or parts of the white columns on both sides. It may start in the subpial zone, and straggle into the white or the gray matter of the brain or cord, as the case may be. It may suddenly end in apparently normal nerve substance, but tracking from the pia into and out of nerve tissue

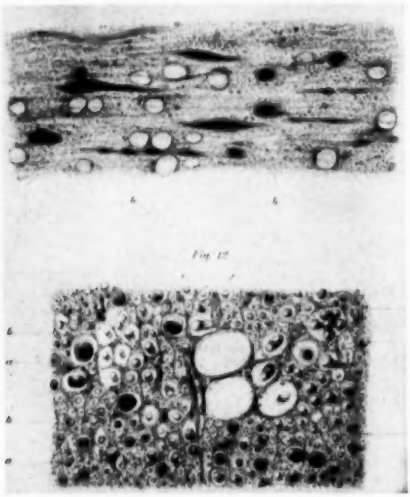

Fig. 4.—Wallerian degeneration. Reproduction of engraving by Frommann [29] (1864), showing the empty spaces and swollen axis-cylinders, in transverse and longitudinal sections.

was seen by Niimi and Kimura [5] (Korea), and later, many times, by Yamagiwa and Shoho [6] (Japan), and by us in the Ceylonese goats.

Other pathologic features which are unnecessary to discuss in this general account may be briefly mentioned. There is little general vascular dilatation and absence of thrombosis. There are no inclusion bodies in the cytoplasm or nuclei of neurones, glia, vascular endothelium, or ependyma. Special stains have not revealed any bacteria or parasites, such as Toxoplasma, Encephalitozoon, Sarcosporidia, yeasts or fungi. Vessels around softened areas may appear more prominent, owing to a greater concentration and increase of reticulin fibers in their walls. In the liquefied zones all structures disappear, but at the edges of such lesions there may be an intense astrocytic proliferation and fibrillary gliosis, a change which becomes increasingly prominent in the more chronic lesions. Clinically silent or healed lesions are discussed later.

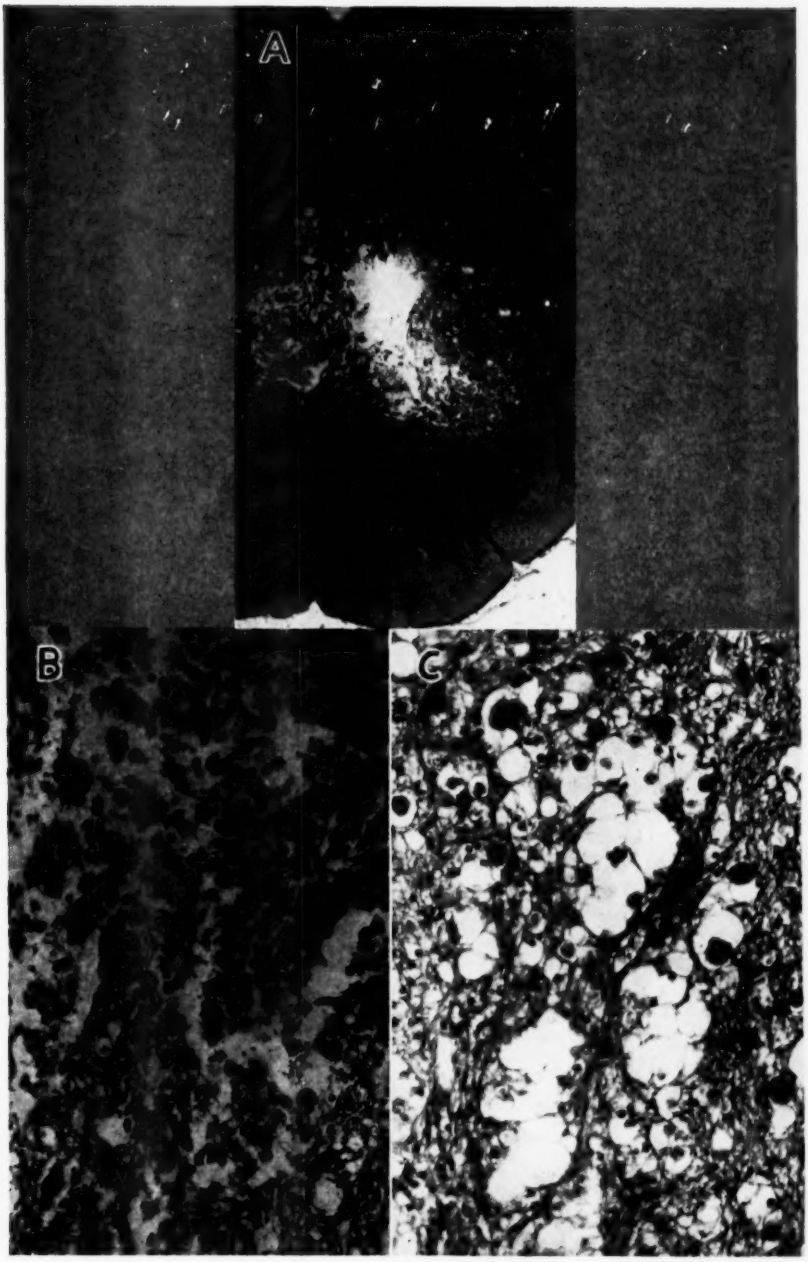

Fig. 5.—Nematodiasis in the sheep (Japan).

A, asymmetrical cavitated area in the midbrain involving the red nucleus. Hematoxylin-eosin stain; × 10.

B, lesion in the spinal cord in case other than that of *A*, showing an area of massive *gemästete Glia* formation. Hematoxylin-eosin stain; × 105.

C, edge of lesion, showing large swollen axis-cylinders, identical with those in Figure 3. Hematoxylin-eosin stain; × 200.

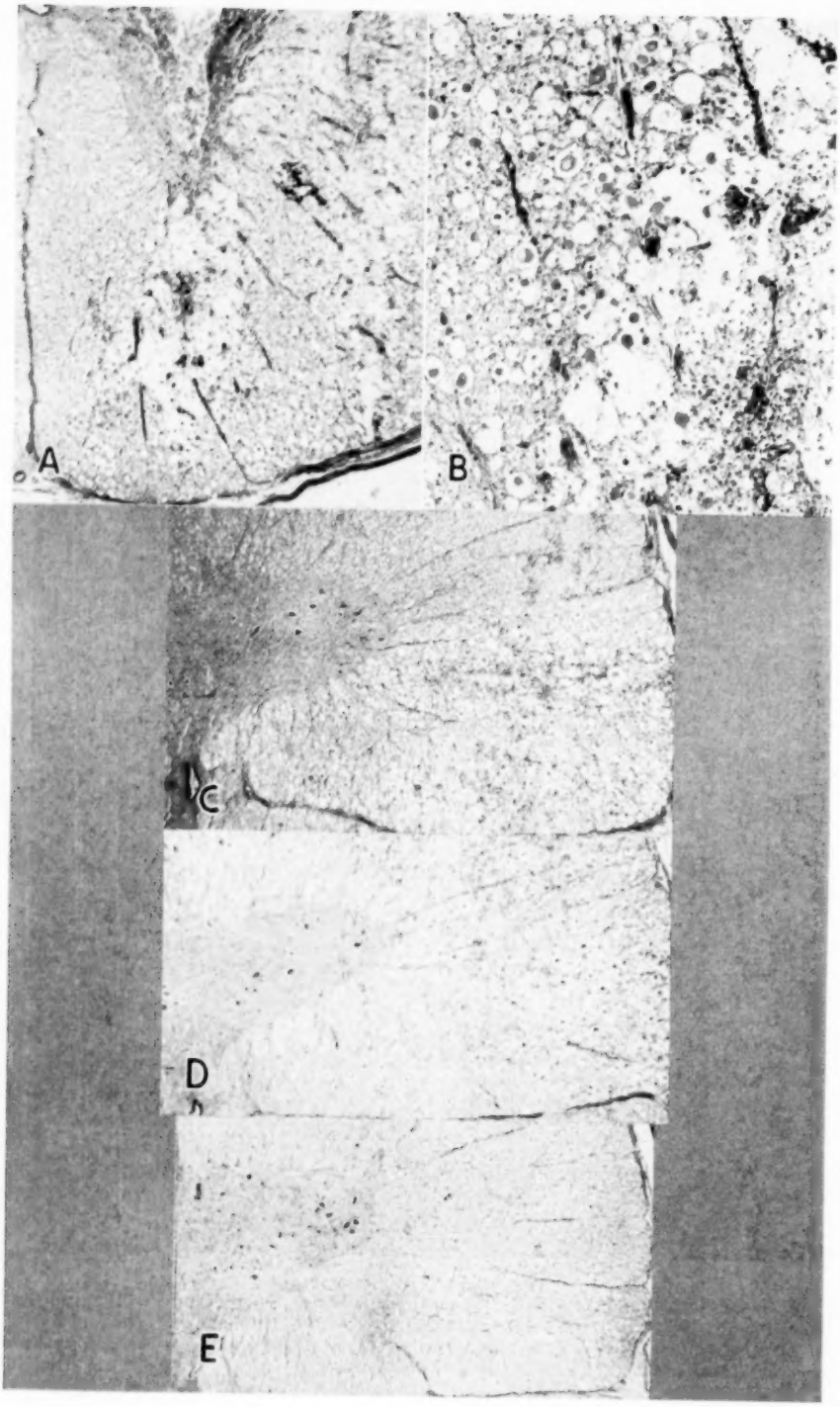

Figure 6

(See legends on opposite page)

ETIOLOGY

The cause of the disease in sheep, goats, and horses was established as an immature nematode (Setaria digitata) by the Japanese, from a study of naturally occurring infections, followed by the crucial method of experiment. A full account of the work in sheep and goats is given in the Special Korean Research Commission Report (1939-1943), while experiments on horses have been reported by Itagaki and associates[15] (1946-1947) and on goats by Ishii and associates[16] (1952).

Setaria digitata (Syn. S. cervi) is a filarial worm, the natural host of which is cattle, in the peritoneum and mesentery of which it lives, without producing any pathological effect. Most textbooks on parasitology, e. g., Cameron[16] (1934), Mönnig[17] (1941) and Chandler[18] (1950), admit ignorance concerning the life history of this species, as well as of the other species, viz., Setaria equina, Setaria labiatopapillosa, and Setaria marshalli, particularly with regard to its pathological significance. The complete range of hosts of these worms is uncertain, but they produce living microfilariae, and an intermediate arthropod host (mosquito) is essential. Setaria spp. may have an almost ubiquitous distribution throughout the world, certainly in the Orient, including Ceylon and India. S. digitata is a common parasite of cattle in the United States, and Chandler states that Stomoxys calcitrans may also be an intermediate host; if true, this may be of importance from the standpoint of the occurrence of the disease in the United States and elsewhere. S. digitata has sometimes been confused with S. labiatopapillosa, which has been recognized as a widely distributed parasite in cattle (and other Bovidae and Cervidae). The

15. Itagaki, S.; Taniguchii, M., and Kawata, M.: Paralysis of the Hind Quarters of Foals: (Filariasis of CNS of Horses), J. Jap. Vet. M. A. **3**:79, 1946; **4**:73, 1947; **4**:105, 1947.

16. Cameron, T. W. M.: The Internal Parasites of Domestic Animals: A Manual for Veterinary Surgeons, London, A. & C. Black, Ltd., 1934, pp. 14 and 217.

17. Mönnig, H. O.: Veterinary Helminthology and Entomology: The Diseases of Domesticated Animals Caused by Helminth and Arthropod Parasites, Ed. 3, Baltimore, William Wood & Company, 1947.

18. Chandler, A. C.: Introduction to Parasitology, with Special Reference to Parasites of Man, Ed. 8, New York, John Wiley & Sons, Inc., 1950.

EXPLANATION OF FIGURE 6

Fig. 6.—Experimental needle-puncture trauma in the spinal cord of the sheep. With use of local anesthesia, a sterile lumbar needle was inserted between the second and the third lumbar vertebra and deliberately thrust into the spinal cord; the animal was paralyzed in the hindlimbs, with greater hypotonicity of the muscles on the right side. The sheep was killed after five days of paralysis; no hemorrhage was visible at the site of trauma, but a discrete focus of greenish-yellow malacia was seen in the cord between the second and the third lumbar segment. Eighteen separate blocks were cut from the lumbar cord, chiefly immediately above and below the focus, but also from the 1st cervical, 7th cervical, 12th thoracic, and 5th and 6th lumbar segments. No signs of secondary degeneration appeared in the 12th thoracic or the 6th lumbar segment.

A, section through the focus, showing immense damage to the ventrolateral columns of the white matter and the ventral horn of the gray matter, liquefaction and cavitation, and massive perivascular and focal leucocytic infiltration. Hematoxylin-eosin stain; × 100.

B, section at the edge of *A*, presenting an appearance like that in Figures 3 and 5, with many swollen axis-cylinders. Hematoxylin-eosin stain; × 200.

C, level of the cord about 2 mm. below *A*. Note lessening intensity of malacia in the ventral columns of the white matter; many swollen axis-cylinders can be seen even at the magnification used. Hematoxylin-eosin stain; × 100.

D, level of cord about 2 mm. below *C*, showing little inflammatory reaction, but still much secondary degeneration. Hematoxylin-eosin stain; × 100.

E, level of cord about 2 mm. below *D*. Note how secondary degeneration has almost disappeared; only a scattered fiber here and there shows swelling of the axis-cylinder. Hematoxylin-eosin stain; × 100.

male measures 30 to 40 mm. in length and 0.35 to 0.5 mm. in thickness; the female, 40 to 120 mm. in length and 0.5 to 0.86 mm. in thickness; but no measurements are given for the microfilariae in the blood, and nothing is noted about the pathogenicity (Baylis,[19] 1939, and Chandler.[18]) The Japanese workers have filled in many of the gaps in the life history, and it is to be hoped that a publication in English will appear dealing with the helminthological aspects.

Microfilariae produced by the female of S. digitata invade the blood of cattle and are transmitted in the mosquito season by the vectors to fresh natural hosts (cattle), in the adults of which the occurrence of a nervous disease has not been recorded. The Korean report indicates that the insect vectors are Anopheles hyrcanus sinensis[20] and Armigeres obturbans[20] (Niimi, report of the Korean Commission), and Aedes togoi[20] has been shown by Itagaki to be concerned with transmission of larvae which produce the equine paralysis. A. obturbans (syn. A. subaltus [Coquillet]) was used by Ishii and associates[19] in their experiments with goats. The microfilariae in the mosquito mature in about two weeks, reaching the salivary glands as infective larvae. Subsequent to the transfer of these larvae by the mosquito into an unnatural host, there is a latent period of about one month before the appearance of neurological signs in affected animals, i. e., until the worm(s) migrates to the craniovertebral canal. (Microfilariae of S. digitata do not appear in the blood of unnatural hosts, a fact which is not surprising, for very often only one worm finds its resting place in the nervous system, and without both male and female the life cycle terminates.) This incubation period was noted particularly in sheep which were affected after being imported into Korea from Australia[21]; the observation has been confirmed repeatedly in Japanese experimental work, although the latent time has been more variable, e. g., from 15 to 66 days in some experimental horses (Itagaki and associates,[15] 1946-1947) and 14 to 33 days in experimental goats (Ishii and associates,[19] 1953). This latent period is an important feature in relation to the possible occurrence of the disease elsewhere in animals (or man?), for signs might not be apparent until winter in temperate zones if man or animal had been bitten by the vectors in the late autumn. The path taken by larvae from the site of cutaneous mosquito inoculation is unknown, although we think it is direct wandering through tissue, for the worms leave no trace before they emerge in the craniovertebral cavity, to penetrate the meninges and nerve tissue and there produce the malacia. The visible pathological damage has been described, and it has been intimated that in some cases the lesion itself may be difficult to find, certainly in an animal such as the horse. The relation between the nematode cause and the pathological effect was established by the Japanese (first suggested, but not published, by Fujita; but suspicions of such an origin were voiced even before 1939) in all the affected species; yet there were difficulties in establishing this. In many cases in which immature worms were found in cases of paralysis, one focus was usually present, and but rarely two or more. The parasite, like many filariae, may have tissue-wandering propensities, and thus may not be found in the focus of softening, but may have traveled out of

19. Baylis, H. A.: Nematoda: The Fauna of British India, Ceylon, and Burma, London, Taylor & Francis, Ltd., 1936, Vol. 2, p. 29.

20. Also vectors of Japanese B encephalitis.

21. This same latent phenomenon was noted 50 years ago in the case of Australian horses being imported into India and becoming affected with spinal paraplegia-so-called Kumri (Macalister [8]).

the nerve tissue subsequent to the production of the trauma and be found free in the craniovertebral canal. In the search for worms at autopsy, therefore, Niimi filtered cerebrospinal fluid through gauze as part of his technique. Furthermore, and of the utmost significance, he found in some cases that the worm might leave the nervous system after the brain and cord had been placed in fixative and might be found in the fixing fluid. To the problem of detection of the lesion in the nervous system there is added that of finding the causal worm, and success in this search is bound up with the duration of the disease in the cases selected. For the most fruitful search for the parasite in the nervous system, cases should be selected in which the disease has been of acute onset and of a few days' duration. Worms may be found in association with the malacia in only 30 to 40% of cases, and in animals which linger on for a few weeks or recover worms may not be found, for the para-

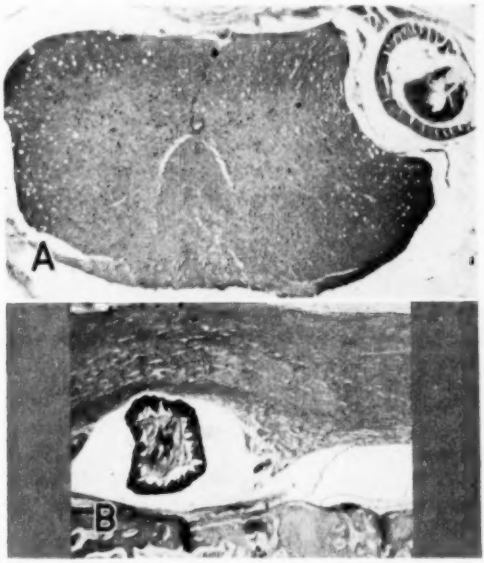

Fig 7.—Experimental lesion of the spinal cord (von Brand and Cullinan [26] with nematode larva; by courtesy of Dr. T. von Brand).

A, spinal cord of rat artificially infected with immature larvae of Eustrongylus sp., with paralysis and death after three days. Note transverse section of a larva compressing the white matter.

B, longitudinal section of vertebral canal of chicken similarly infected, with death in 24 hours. Note larva compressing the cord.

sites may wander away, die, and disintegrate and only fragments of a hyaline capsule may be found. (The difficulties attending clear identification of nematodes in the last-mentioned state are notorious; see Figure 8*D* and compare the work of Wilder [22] (1951) on human nematode endophthalmitis.) In Figure 8*A* to *C* typical lesions with the parasite present are shown.

The disease has been reproduced by Japanese workers in all the species affected under natural conditions. After the mosquito vectors were fed on cattle (natural

22. Wilder, H. C.: Nematode Endophthalmitis, Tr. Am. Acad. Ophth. **55**:99, 1950.

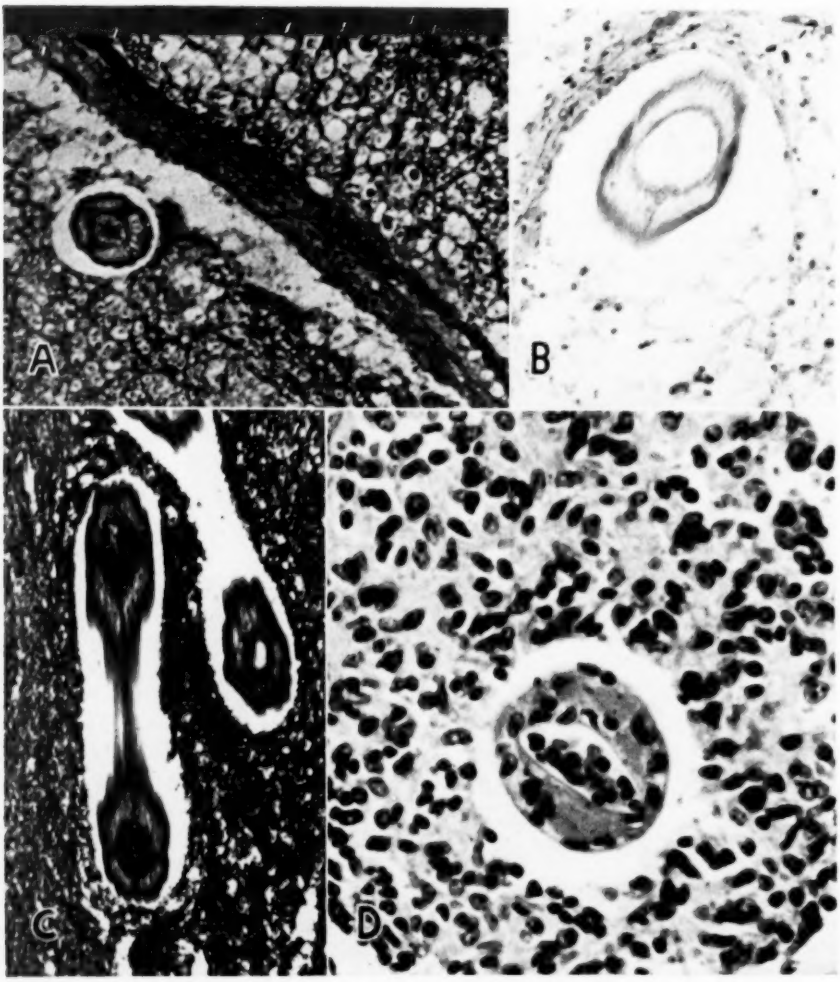

Fig 8.—*A-C*, spinal cord of sheep (Japan) with nematodiasis. *A* and *B*, sections through central part of a malacic focus, showing presence of nematode, cut transversely. Hematoxylin and eosin stain; *A*, × 90; *B*, × 200.

C, cerebellar white matter from a case other than that of *A* and *B*, showing presence of immature Setaria, cut obliquely. Hematoxylin-eosin stain; × 90.

D, spinal cord of goat (Ceylon) with nematodiasis, illustrating difficulty of identification of nematodes. This lesion was present at the edge of a malacic focus (Figs. 2 and 3*C*); it is a granulomatous focus with a central object, which is clearly not a neural structure or a foreign body, and contains host cells. A remnant of hyaline capsule is suggestive evidence, but unequivocal identification of a worm is impossible. Hematoxylin-eosin stain; × 400.

hosts) harboring the microfilariae of S. digitata in their blood, the insects were kept for 14 days to allow the maturation of infective larvae. The latter were dissected out of the insects and inoculated, by hypodermic needle, subcutaneously into the various species. Typical paralytic symptoms, lesions, and parasites were identified in positive clinical cases.

The cycle of investigation with respect to the proof of the nature and cause of this disease (now called cerebrospinal nematodiasis), which has been known as a clinical entity for many years, was thus completed, starting with direct observation and finishing with the experimental biological method. At our instigation, McGaughey [23] (1951) has identified causal worms in paralyzed goats in Ceylon; hence no doubt can remain regarding the identity of the caprine form with the Japanese disease.

COMMENT

General Considerations.—The identification of a helminthic cause of a specific nervous disease opens a fresh chapter in the history both of pathology and of helminthology. There have been many reports of the finding of a variety of helminths in the nervous system, both in man and in animals, associated with neurological signs, but such cases are rare (Beautyman and Woolf,[24] 1952; Koizumi,[25] 1952). This condition of cerebrospinal nematodiasis in animals, however, would seem to represent an entity, occurring in enzootic (or epizootic) proportions and caused by the invasion by nematodes of unnatural hosts (sheep, goats, and horses), in which they behave in an anomalous way, by a final assault on the nervous system. Relevant experimental observations support our view that the nervous system may be a favored anatomical site for parasites in unnatural hosts. Von Brand and Cullinan [26] (1943), for example, transplanted larvae of Eustronglyides, taken from fish, in which they reside in the liver and mesenteric fat (adult-stage natural hosts being birds), into subcutaneous pockets of rats and chickens; in both species larvae invaded the nervous system and paralyzed and killed many of the experimental hosts (Fig. 7*A* and *B*). Studies by Tiner [27] (1951) provide further evidence on this point, for he showed that infection of mice by ascarids obtained from raccoons resulted in a 100% mortality from damage to the brain. Consequently, the question of what helminthic parasites do in unnatural, as compared with natural, hosts may be the crux to certain disease problems. Yet a Gordian knot may have to be unraveled in this connection. The original name given the disease by the Japanese—setariasis—we have changed to nematodiasis, for we are of the opinion that other nematodes may behave in the same way in unnatural hosts; i.e., the same pathological disorder, present in different animal species, including man, may have a multiplicity of helminthic causes. S. equina (natural host, horse) might conceiv-

23. McGaughey, C. A.: Necrotising Encephalomyelitis of Goats in Ceylon: A Note on the Occurrence of Nematode Larvae in the Brain and Spinal Cord, Brit. Vet. J. **107**:449, 1951.

24. Beautyman, W., and Woolf, A. L.: An Ascaris Larva in the Brain in Association with Acute Anterior Poliomyelitis, J. Path. & Bact. **63**:635, 1951.

25. Koizumi, H.: Human Parasitology, Iwanami Series, 164, Tokyo, 1952 (in Japanese).

26. von Brand T., and Cullinan, R. P.: Physiological Observations upon a Larval Eustrongylides: The Behavior in Abnormal Warm-Blooded Hosts, Proc. Helminthological Soc. Washington **10**:29, 1943.

27. Tiner, J. D.: Observations on Larval Carnivore Ascarids in Rodents, J. Parasitol. (No. 5, Pt. 2) **37**:21, 1951.

ably produce the same disease if mosquito-stage larvae were transimtted to other species. Although it has not been found that neural nematodiasis is caused in adult cattle by S. digitata, the possibility of its occurring under certain abnormal conditions, or of other nematodes causing the same disease, can not be excluded. One of us (C. S.) has found that there may be intrauterine infection of the fetal calf by Setaria spp. and that this may be involved in the production of so-called blindness and paralysis in newborn and young calves in Japan.

Nature of Neural Lesion: Comparison with Experimental Trauma and Wallerian Degeneration.—It is plain that the extent and nature of the damage to the nerve tissue in fully developed malacic foci, as described above, are such as to be incontestibly responsible for a paralytic disease in the living animals involved. The variability in anatomical location and severity of the focal malacia, with concomitant eosinophilic meningitis (and radiculitis), is in agreement with the diversity of clinical signs which have been observed in a large number of cases.

A consideration of the pathology of the acute malacic disease indicated a complete dissimilarity to that of any of the disseminated encephalitides caused by viruses, to that of the more suppurative or granulomatous lesions caused by bacteria, or to that of any protozoan or mycotic disease. The absence of vascular changes in this disease precludes its being related to certain types of hemorrhagic encephalopathy assumed to be due to a toxic or an allergic factor. It is not a focal demyelinating disease per se, for all structures involved (myelin, axis-cylinders, nerve cells, and glia) finally disintegrate, and in the brain the lesion may initially involve gray matter. The process is one which follows a relatively rapid destruction of nerve tissue, but in a palpably restricted track, in which normal structure in the center is completely obliterated by liquefaction, with resultant irregular areas of microcavitation. The latter may, however, extend in some cases and be visible to the naked eye, although the lesion never becomes really gross and porencephalous. Some of the inflammatory reaction may simply be a result of acute tissue dissolution, and perhaps nothing more, for it is not proved that the causative nematodes produce any toxin. These contentions are supported by the similarity to lesions observed in uncomplicated mechanical trauma.

The unmistakable huge swellings of fragmented axis-cylinders, which lend to the composite lesion such a highly characteristic feature, should be emphasized, although they are not diagnostic of nematodiasis alone. They are well known to neuropathologists, although they are never pictured in textbooks of neuropathology; but they may occasionally have been mistaken for such structures as myelin balls, or corpora amylacea. They represent a classic example of the acute stage of secondary, or Wallerian, degeneration in an ascending and a descending direction (drawings, Ramón y Cajal,[28] 1928). An exact analogy can be found in the lesions of acute traumatic transverse myelopathy in man and dogs which die in a few days. It has, furthermore, been possible to produce almost a replica of the focal malacia, with its secondary degeneration, by experimental stab wounds (with a sterile needle) in the spinal cord of the sheep (Fig. 6*A* to *E*). In one animal, paralyzed for five days after a spinal stab wound, the acute type of lesion was produced almost in its entirety, except for the eosinophilic infiltration; in another experimentally para-

28. Ramón y Cajal, S.: Degeneration and Regeneration of the Nervous System, London, Oxford University Press, 1928, Vol. 2, p. 493.

lyzed sheep, kept alive for four weeks, the lesion was in a more chronic stage; there was well-developed surrounding gliosis, but swellings of the axis-cylinders were still very prominent. (As a matter of historical interest, an engraving from one of the earliest studies on myelitis and secondary degeneration, by Frommann [29] [1864], is reproduced [Fig. 4]).

There was, thus, evidence, from various sources, that the cause of the paralysis in domesticated animals in the Far East might be linked with a factor which could be simulated by simple mechanical trauma. This is in harmony with established facts concerning the cause of the disease, namely, that the malacia (with or without eosinophilic meningitis) is produced by the entrance and wandering of a nematode(s) in the craniovertebral canal. The occurrence of patchy eosinophilic meningitis (dural or leptomeningeal), and even radiculitis, not necessarily restricted to parts overlying the focal malacia in the central nervous system, is therefore not surprising, and is evidence for the direct migratory path of the worm into the craniovertebral cavity, perhaps along a nerve.

Multiple Foci and Reinfection.—From a clinical and pathological standpoint, there are ample data to indicate that a variety of events may follow the entrance of a nematode into the craniovertebral cavity of an animal host. 1. The worm may produce a mild meningeal and radicular inflammation, in which there may be a preponderance of eosinophiles, and which may cause only slight, transient clinical signs of weakness or incoordination. 2. The worm may then invade the nervous system, but produce a minute focus in some less vital part (lower regions of the cord). This event might explain those cases in which there is a mild degree of paralysis and recovery or in which the lesion may be clinically silent, e. g., the cases of horses described by Tanaka and associates.[7] 3. The worm may produce the classic focus of malacia which has been described and is responsible for signs of acute ataxia and paralysis. 4. A single worm may produce one malacic lesion, or it may produce several by its irregular wandering. 5. If more than one worm enters, multiple lesions may be expected, which need not be all of the same age. All these phenomena have been observed by Shoho and Tanaka [30] (1952).

It is known that animals may show slight clinical signs one season and then either recover completely or show some permanent residual neurological effect, such as a limping gait or a drooping ear or eyelid, and the following year, or even later in the same season, exhibit signs of acute, and perhaps fatal, paralysis. It might therefore be deduced from clinical evidence that reinfection can occur, and may be commoner than is suspected. This is supported by pathological studies, for there may be found in the nervous system in the same case a lesion of acute malacia, with its classic secondary degeneration, in one part and older lesions in another. In the older lesions parasites are usually absent; there may still be eosinophilic infiltration, and there is usually sclerosis around the small cavitated area; pigment-bearing *gemästete Glia* may be numerous. This lesion will be discussed elsewhere by Shoho and Tanaka.[30]

All these variations are of significance. They emphasize many of the complexities associated with the pathogenesis of the disease, which may have been responsible

29. Frommann, C.: Untersuchungen über die normale und pathologische Anatomie des Ruckenmarks, Jena, F. Frommann, 1864, p. 128.

30. Shoho, C., and Tanaka, T.: Unpublished data.

for much of the confusion concerning the true identification of cerebrospinal nematodiasis in the Far East, in the past, and may still be so. This may become of importance whenever the problem of pathoiogical diagnosis arises in connection with neurologic disorders of animals (and man) in other parts of the world which might be of the same nature.

Control of the Disease by Filaricide Drugs.—The discovery of the high efficiency of 1-diethylcarbamyl-4-methyl piperazine as a filaricide (against Wuchereria bancrofti) gave a clue to a possible chemotherapeutic control of cerebrospinal nematodiasis (Shoho,[31] 1952). (This drug has an almost immediate effect on the microfilaria count in the blood of cattle carrying S. digitata.) The results of a preliminary field trial by Shoho suggested that the disease could be prevented in sheep by oral administration of a dose of this drug (20 to 40 mg. per kilogram of body weight) on two successive days, at fortnightly intervals, during the height of the summer months, when the disease is expected to appear in known areas in Japan. Furthermore, in many animals (sheep, goats, and foals) observed within a day of the onset of incoordination and motor weakness (i.e., presumably before acute damage of nerve tissue had occurred, and when perhaps, only meningeal and radicular reaction was present), a complete cure could be effected by comparable doses of the drug. These observations on the effect of a specific filaricide drug are additional evidence that the disease is caused primarily by a filaria. Strange to say, arsenical and antimony compounds and santonin were suggested 30 years ago as a possible cure for so-called kumri (paralysis of horses in India), which we believe is nematodiasis, though at that time neither the pathology nor the cause of that disease had been clearly defined. However, in areas where nematodiasis is an important enzootic problem, the solution of control under ideal conditions might lie in elimination of Setaria from the reservoir of infection (i.e., cattle). This would be a formidable task, and more information is required on the pharmacological action of the drug on domestic animals.

Possible Occurrence of Cerebrospinal Nematodiasis in Animals in Other Parts of the World.—We do not suggest that nematodiasis is an etiological answer to all unsolved nervous diseases in animals (and man). The facts, as presented in this paper, must speak for themselves.

That nematodiasis of the nervous system has not been considered before in connection with certain paralytic disorders of domesticated animals is not astonishing; one might ascribe it to the general neglect of the nervous system by veterinary pathologists at large. We have indicated how meticulous must be the neuropathological examinations for identification of the lesion and the causal worms. In many countries the presence of virus encephalitides in animals may have overshadowed the existence of many other nervous diseases, especially if too much reliance was placed on clinical diagnosis, because doubtless all paralysis in animals would then be regarded as due to infectious encephalitis. In Japan, cerebrospinal nematodiasis was confused for years with virus encephalitis, and still may be so (there and elsewhere), for neutralization tests may be positive in the presence of a concomitant helminthic infection.

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31. Shoho, C.: Chemotherapeutic Control of Cerebro-Spinal Nematodiasis by 1-Diethylcarbamtyl-4-Methylpiperazine Citrate, Brit. Vet. J. **108**:134, 1952.

Neural nematodiasis is, therefore, a disease possibly occurring in domesticated (and wild) animals in parts of the world (*a*) where cattle carrying S. digitata exist as natural hosts, (*b*) where suitable insect vectors abound in the proper season (and these may not be the same as in Japan; see the suggestion by Chandler [18] that Stomoxys calcitrans is an intermediate host in the United States), and (*c*) where other animals live in the same area as potential unnatural hosts. The possibilities then become immense. S. digitata is known to infect Bovidae as natural hosts in some parts of Europe at least, in India, in nearly all regions of the Orient, and in North America. In the Far East, it would seem unlikely for the disease to be confined to Korea, on the Asiatic mainland (and not to occur in China, Siam, Assam, or Burma), and to Ceylon and Japan, as islands. In India and Persia there have been repeated reports for many years of an enzootic seasonal paralysis of goats; the pathological descriptions do not suffice to indicate the exact nature of the disease, and the cause has never been determined, all attempts to identify an infectious cause having been futile. Before the turn of the century there were similar reports of an enzootic paralysis of deer in Germany; again, the clinical and pathological descriptions were scanty, but one author actually found Setaria (designated as S. labiatopapillosa) in the spinal canal of a paralyzed deer. His descriptions of the condition are reminiscent of unpublished observations on paralysis of deer in Texas and California. Monlux [32] (1951), for example, in one such case observed a solitary hemorrhagic malacic focus in the spinal cord (fifth to sixth cervical segment), which could not be distinguished from the lesion in nematodiasis, but worms were not found. There have been numerous other descriptions of peculiar paralysis in wild animals, e. g., in moose (King,[33] 1939); Fenstermacher and Jellison,[34] 1933), in wapiti, Peking sikas, and yaks (Whitehead,[35] 1950)—all of undetermined cause; such reports could bear investigating, with the idea of a helminthic cause in mind.

Reference must be made to so-called kumri (a Hindustani word meaning "weakness of the loin"), a paraplegia of horses which has occurred in India, Burma, and China for at least 100 years (Macalister [4]). This disease has long been known to occur as a seasonal enzootic; while, obviously, it may have been confused with other conditions causing motor weakness, there can be little doubt, from the descriptions, of its specific clinical nature. Unfortunately, there is little in the literature which accurately defines the pathology, although some old reports by English veterinarians indicated that macroscopic areas of softening were found in the spinal cord. Indeed, worms (sometimes classified as Setaria) were actually found free in the spinal canal in some cases many years ago, but they were thought to be accidental invaders (Macalister [4]). There were also shrewd observations regarding treatment by arsenicals and antimony compounds (anthelmintics), which might have been a clue to the helminthic cause, but these apparently escaped further study. An even more bizarre fact, exemplifying how the origin of observations in the past may become part of the limbo of forgotten things, can be found in Railliet [3] (1895). Apparently, a similar paralysis of horses was known in Europe at that time; the causal worm

32. Monlux, W. S.: Unpublished data.

33. King, L. S.: Moose Encephalitis, Am. J. Path. **15**:445, 1939.

34. Fenstermacher, R., and Jellison, W. L.: Diseases Affecting Moose, Bulletin 294, Minnesota Agricultural Experiment Station, 1933.

35. Whitehead, G. K.: Deer and Their Management in the Deer Parks of Great Britain and Ireland, London, Country Life, Ltd., 1950.

was called Filaria haemorrhagique, and Railliet gives crude drawings of the spinal cord indicating the presence of lesions, which were not, however, described. It is also strange that the word kumri (or kumree) was used by veterinarians to describe a paralysis of horses in England in the early part of the 19th century. Hence it might be questioned whether the disease occurred then in Europe but disappeared, just as malaria did in human beings. There is also a clear analogy to kumri to be deduced from the described facts concerning so-called "wobblers" among foals in the United States. In a pathological study by Olafson[36] (1942) there are pictures which present evidence of the secondary degeneration, such as is found in nematodiasis below a malacic focus in the spinal cord, although its real nature was not determined then. Col. T. C. Jones, Veterinary Corps, Armed Forces Institute of Pathology, Washington, D. C., intimated, in a private communication, that in "wobblers" there might be a patchy eosinophilic, hemorrhagic meningitis and radiculitis with secondary degeneration in the cord, but that exhaustive examination of the cord from affected horses, such as was performed on our goats, had not yet been made.

Thus, a large body of inferential data points to the possible existence of cerebrospinal nematodiasis in animals all over the globe, although different species of nematodes may be involved etiologically. Kennedy, Whitlock, and Roberts[37] (1952), for example, described a paralytic disease in sheep in which the clinical history and pathology were entirely identical with those of cerebrospinal nematodiasis but were caused by a new species of nematode—designated by them as Neurofilaria cornelliensis.

Possible Occurrence of Cerebrospinal Nematodiasis in Man.—Our concept that neural nematodiasis may exist in man rests on the evidence that the animal disease results from the invasion of the nervous system by nematodes (natural host, cattle) into unnatural hosts, in which category man definitely belongs.

On the basis of the pathological findings in animals, it might be helpful to sketch hypothetically a clinical history of a human case, which might act as a diagnostic filter. 1. The disease must show a seasonal tendency coinciding with the "insect" season, although neurological signs might not appear until after the hot weather was over. 2. The disease might affect either sex but might predominate in young adults. 3. The occurrence of the disease might coincide with that of other mosquito-borne diseases. 4. Clinically, there might be a hyperacute (dramatic) or subacute onset with motor weakness, ataxia, and paralysis, as in transverse myelitis, but with few constitutional signs or fever; the neurological signs might vary from case to case, as is consistent with a haphazard distribution of the disease process. 5. The disease might be endemic in some parts. 6. The various virus encephalitides would have to be excluded, but the possibility of confusion might still be borne in mind. 7. Tests of the cerebrospinal fluid would be negative for viruses and bacteria, but there might be pleocytosis, with many eosinophiles. 8. Microfilaria would not be present in

36. Olafson, P.: Wobblers in Foals Compared with Ataxic (Swayback) Lambs, Cornell Vet. **32**:141, 1942.

37. Kennedy, P. C.; Whitlock, J. H., and Roberts, S. J.: Neurofilariosis, a Paralytic Disease of Sheep: I. Introduction, Symptomatology, and Pathology, Cornell Vet. **42**: 118, 1952. Whitlock, J. H.: Neurofilariosis, a Paralytic Disease of Sheep: II. Neurofilaria Cornellensis, N. G. N., Sp. (Nematoda, Filarioidea), a New Nematode Parasite from the Spinal Cord of Sheep, ibid. **42**:125, 1952.

the blood. 9. Sufficient indication of the pathological picture has been given that, provided a thorough examination of the nervous system had been made, pathological diagnosis would present little difficulty. The difficulty encountered in the detection of worms in the animal disease indicates that they might not be found unless the patient died in the acute stage. 10. If a human form does exist, the worms might frequently attack the spinal cord, and the lesion might be unilateral. If this happened, other issues might arise, for the patient might then present acute neuroparalytic signs, recover with slight residual defect and clinical diagnosis thereafter be rendered impossible unless skin and complement fixation tests could be developed as diagnostic aids (Bosicevich,[38] 1951).

Articles have been found in the neuropathological literature in which the available data are reminiscent of those on the animal disease, although we realize these may not be reliable. Our experiments on traumatic malacia suggest that in some cases of suspected transverse myelitis in which a history of accident or infection is impossible to trace, the possibility of this disease may be borne in mind. Cases of reputed multiple sclerosis, in which there had been predominant, localizing spinal signs and in which no exacerbations occurred after the first attack and remission, might also be remembered. Some of the descriptions of subacute necrotizing myelitis (Wilson,[39] 1940) and multiple degenerative softenings in the spinal cord (Hassin and Bassoe,[40] 1922) remind one of nematodiasis. Perhaps the most suggestive medical reports we have found, however, are those of so-called eosinophilic meningitis, with focal areas of softening in the nervous system of undetermined cause (Ferguson, McVay, and Hill,[41] 1950, and the following discussion by Sheldon[42]). In the review by Chalgren and Baker,[43] in the chapter on parasitic diseases involving the nervous system there is no mention of any disease comparable to animal nematodiasis.

Perhaps more, indirect, support for our theory arises from observations of Wilder[22] (1950) on human nematode endopthalmitis in the United States. For 46 eyes of children and adolescents received at the Armed Forces Institute of Pathology, Washington, D. C., from many parts of the United States, a variety of diagnoses had been made; all eyes showed some feature of eosinophilic abscess or granulomatous endophthalmitis. In none of the original sections were helminthic parasites present. On the basis of the resemblance of the lesions to some in animals caused by worms, reexamination by serial sections was made. The presence of larvae was revealed in 24 eyes, and in the remaining eyes the lesions were so uniform as to justify a diagnosis of nematode endophthalmitis in all. It is noteworthy (compare difficulties in nematodiasis) that Wilder performed the heroic task of examining

38. Bozicevich, J.: Immunological Diagnosis of Parasitic Diseases, in Infections in Man, edited by H. Most, New York, Columbia University Press, 1951.

39. Wilson, S. A. K.: Neurology, edited by A. N. Bruce, London, Edward Arnold & Co., 1940, Vol. 2.

40. Hassin, G. B., and Bassoe, P.: Multiple Degenerative Softening Versus Multiple Sclerosis, Arch. Neurol. & Psychiat. **7**:613, 1922.

41. Ferguson, R. L.; McVay, C. B., and Hill, J.: Eosinophilic Meningitis: Two Case Reports, Am. J. Path. **26**:725, 1950.

42. Sheldon, W. H., in discussion on Ferguson, McVay, and Hill.[41]

43. Chalgren, W. S., and Baker, A. B.: Tropical Diseases. Involvement of the Nervous System, Arch. Path. **41**:66, 1946.

2,300 serial sections of one eye before a single larva was found, and this was contained in 12 sections. Although the exact species of nematode was not identified, it was thought that they might be third-stage hookworm larvae. Wilder concluded that nematodes might play a hitherto unrecognized role in blindness in children, particularly in the production of "pseudoglioma" and Coats's disease. A path of entry into the eye from the cranial cavity was not considered, but, whatever the worm might be, neural tissue might also be a locus of attraction, just as much as the eye. This may seem particularly evident if we consider in this connection the problem of ocular filariasis in animals, which might be an analogue of Wilder's human endophthalmitis. "Worm-in-the-eye," caused by Setaria, has been known for generations to occur in horses in India and many other countries in Asia, as well as in Europe, although there are no pathological reports, and there has always been some confusion regarding the species of Setaria involved. (This condition is amenable to surgical removal of the worm.) Many of the older reports from India expressed the belief that the ocular disease might be related to the problem of spinal paraplegia (kumri), for some animals apparently show symptoms of both or one following the other (Macalister [4]). Recent work in Japan suggests a similar dual disease problem of neural and ocular (and conjunctival) filariasis caused by Setaria. The idea of a complex of a helminthic disease affecting the eye or the nervous system, entirely dependent on the fortuitous wandering of a parasitic worm, may thus not be fantastic.

Other Problems Arising from a Consideration of Cerebrospinal Helminthiasis.—Beautyman and Woolf [24] reported observations in the case of a child in whom were found an Ascaris larva in the thalamus and acute poliomyelitis of the brain stem. In their opinion these findings indicated that there might be a complex virus-helminth relationship. They also pointed out that there were no neurological signs referable to the larval lesion in the thalamus and that larval migration in the nervous system might occasionally cause focal and generalized epilepsy. They mentioned the paucity of pathological reports on nematode invasion of the nervous system of man (Chalgren and Baker [43]). Many of their speculations receive additional support from the studies on animal cerebrospinal nematodiasis, as we indicate below.

A. Clinically Inapparent, or Masked, Helminthic Infection of the Nervous System: This phenomenon (Beautyman and Woolf) is supported by observations on neural nematodiasis. The malacic lesion is approximately the same size in sheep, goats and horses, and it is obvious that clinical signs would depend primarily on the neuroanatomical location of the focus. In animals with a large nervous system and great length of spinal cord, as in the horse, few or no neurological signs might result if the lesion was located in certain parts of the cerebral cortex or in the lower lumbar region of the cord; minor degrees of neurological impairment might never be diagnosed. A malacic lesion must be the immediate reaction to a nematode; a granulomatous or sclerotic one might be the residual, more chronic, effect, in which the parasite might be dead. Consequently, unless the nervous disease was immediately fatal, and if life was prolonged, neither malacia nor the parasite might be recognizable in animals or in man. Ishii and associates [10] noted, in experimental goats given injections of Setaria larvae, that in some animals which had completely recovered from an acute attack of ataxia, autopsy several weeks later revealed neither lesion nor parasites. Tanaka and associates, in a pathological survey of the brains of 100 horses, found lesions, with and without parasites, in 9 animals in which no clinical signs were seen during life.

The same problem of clinically unapparent nervous disease in the presence of even disseminated encephalitic lesions in lower animals has been raised in the case of experimental allergic encephalitis in mice by Olitsky, Casals and Thal [44] (1950), in guinea pigs by Lumsden [45] (1949), and in other work on the same problem by one of us (J. R. M. I.). Meticulous neuropathological examination in many "neurological" conditions thus becomes imperative.

B. Nematode Infection Facilitating Virus Invasion of the Nervous System: The relation of nematodes to neurotropic virus infections has not been seriously considered. Shope [46] (1943), however, opened the way by his fascinating work proving that the complex pathogenesis of swine influenza was bound up with earthworm, lungworm, virus, and Hemophilus suis. (The work of Syverton [47] and associates [1947] on the association of Trichinella spiralis and lymphocytic choriomeningitis in guinea pigs and that of Castro [48] [1950] on the possibility of helminthic vectors being involved in pathogenesis of poliomyelitis may also be cited). Our surmise that there is a parallel adjuvant relation between S. digitata (and the disease in animals) and Japanese encephalitis B in man is no more a flight of fancy than the speculations of Beautyman and Woolf. Sabin, Ginder and Matumoto [49] (1947), in a study of the epidemiology of Japanese encephalitis B, indicated that the virus was sometimes spread extensively in domestic animals in endemic regions of Japan when human beings were affected very little. The question of how the virus maintains itself in nature during nonepidemic years was considered of profound significance, and they mooted the question of intermediate arthropod and helminthic hosts. The same mosquitoes have been incriminated in the transmission of Japanese encephalitis B in man and of cerebrospinal nematodiasis of animals, hence a possible relationship cannot be ignored.

C. Dual Neurotropic Virus and Helminth Infections: If a helminth lodges in the nervous system, the final outcome will depend partly on its neuroanatomical location and on the survival of the worm to extend damage. That neurological signs in man due to a worm can be masked by a later, or simultaneous, virus infection has been proved by Beautyman and Woolf. In a routine pathological examination of the brains of 69 horses, naturally infected with Japanese (equine) B encephalitis, Sugawa, Mochizuki, and Yamamoto [50] (1949) found a malacic lesion with or with-

44. Olitsky, P. K.; Casals, J., and Thal, C.: Relative Susceptibility of Various Stocks of Mice to Experimental Disseminated Encephalomyelitis, Proc. Soc. Exper. Biol. & Med. **75**:276, 1950.

45. Lumsden, C. E.: Experimental "Allergic" Encephalomyelitis: On the Nature of the Encephalitogenic Agent, Brain **72**:517, 1949.

46. Shope, R. E.: The Swine Lungworm as a Reservoir and Intermediate Host for Swine Influenza Virus: Demonstration of Masked Swine Influenza Virus in Lungworm Larvae and Swine Under Natural Conditions, J. Exper. Med. **77**:127, 1943.

47. Syverton, J. T.; McCoy, O. R., and Koomen, J.: The Transmission of the Virus of Lymphocytic Choriomeningitis by Trichinella Spiralis, J. Exper. Med. **85**:759, 1947.

48. Castro, J. G.: Relaciones mutuas entre melmintos y microbios: Papel vectorias de los helmintos, Rev. ibérica parasitol. **10**:379, 1950.

49. Sabin, A. B.; Ginder, D. R., and Matumoto, M.: Difference in Dissemination of Virus of Japanese B Encephalitis Among Domestic Animals and Human Beings in Japan, Am. J. Hyg. **46**:341, 1947.

50. Sugawa, Y.; Mochizuki, H., and Yamamoto, S.: First Report on Japanese Equine Encephalitis, Bulletin 9, Government Station for Animal Hygiene, Tokyo, 1949.

out setaria in 4. Consequently, we might ask, How often has this happened before? If clinical, and other, evidence seemingly indicated virus encephalitis, then, presumably, little further study might be made of the cases; but with nematodiasis in mind, this finding might be of significance. We believe that in Japan cerebrospinal nematodiasis in animals has often been confused with virus encephalitis. Neutralization tests indicative of the latter could be positive in the presence of a coincidental nematodiasis, or, indeed, the virus infection might be initiated by entrance of a worm into the nervous system. (See work by Findlay and Howard [51] [1950] on the precipitation of poliomyelitis infection by nonspecific stimuli.) It is thus interesting to find in some reports on the pathology of human Japanese encephalitis B, mention of "mushy areas" in the spinal cord, but it is not obvious that these foci received specific histological study. One of us (C. S.) has observed areas of cavitation in the brains of four children reputed to have died of Japanese encephalitis B, pointing to the existence of a coincidental process or an as yet undescribed pathological feature of Japanese encephalitis B.

D. Migratory Paths of Helminths to the Central Nervous System: Beautyman and Woolf discuss this problem with particular reference to the classic work of Yokogawa [52] (1923) and Fülleborn [53] (1921) on Ascaris, and emphasis is perforce laid on intravascular paths. It has generally been believed that ascarids, after the hatching of the eggs in the intestine, go on a "Cook's" tour to the lungs and that some larvae may wander into the general circulation and reach the nervous system or the eyes. Yokogawa's original experimental findings, in which 10 out of 14 mice (given a large number of canine Ascaris eggs) showed hemorrhages in the cerebrum due to migrating larvae, were also interpreted to mean that the route to the central nervous system was via the circulation. We wonder why a direct pathway cannot be considered to account for all cases of involvement of the nervous system. In cerebrospinal nematodiasis it can hardly be questioned that the direct path through tissue is the one taken by the Setaria, for the malacic lesion is not embolic, but resembles one due to mechanical trauma. We might again draw attention to the work of von Brand and Cullinan,[26] who showed that strongylid larvae of fish, when transplanted into unnatural hosts, invaded the nervous system, paralyzing and killing the host. These larvae took the direct route, for one could trace the histological path through connective tissue and muscle, and between vertebral joints to the cord, signposted by the eosinophilic tissue reaction. Similar opinions have been expressed recently by Koizumi [25] in connection with the migration of parasites in abnormal hosts.

Finally, our observations bolster the conviction of the necessity for more extensive study of the pathology of helminthic infections in man and animals. Our concern in this paper has been with the problem of the behavior of migrating worms in unnatural hosts, and with the occurrence, under certain conditions, of a specific nervous disease due to the production of acute and subacute malacic lesions. There

51. Findlay, G. M., and Howard, E. M.: Non-Specific Shock in Experimental Poliomyelitis, J. Path. & Bact. **62**:371, 1950.

52. Yokogawa, S.: On Ascariasis and the Life-History of Ascaris, Tainwan Igakkai Zasshi, p. 241, 1923.

53. Fülleborn, F.: Über Askaridenlarven im Gehirn: Vorläufigse Mitteilung, Arch. Schiffs- u. Tropen-Hyg. **25**:62, 1921.

are other implications, for one should not omit consideration of what migrating larvae, or immature worms, might do in the visceral organs of unnatural hosts, in which more chronic granulomatous lesions could be produced, and even so might involve the nervous system. We might then draw attention to the highly intriguing observations of Jaques [54] (1952) on the etiological role of nematodes in Boeck's sarcoid and to other work by Beaver and associates [55] (1952) on the part played by worms as a cause of chronic eosinophilia.

SUMMARY

A neuroparalysis of sheep, goats, and horses (Japan and Korea) and of goats (Ceylon) has occurred seasonally for many years, and may have appeared in other countries but has evaded true pathological identification.

The lesion is a focal malacia, with or without hemorrhage, proceeding to liquefaction and cavitation, with a haphazard distribution in the nervous system. The neuropathology differs from that of disorders caused by viruses, bacteria, protozoa, fungi, or toxic and deficiency factors. The nature of the process is consistent with the concept that it is essentially due to trauma of nerve tissue produced by a wandering worm; this concept is supported by observations on experimental needle stab wounds in the spinal cord.

The causal agent was proved by Japanese workers to be immature Setaria digitata, the final natural host of which is cattle and into the blood of which microfiliariae are released. The intermediate host is the mosquito, in which the infective larvae develop. When the latter are transmitted to unnatural hosts (sheep, goats, and horses), they migrate to the nervous system and produce the focal malacia with its resultant acute or subacute clinical paralysis.

An identical human disorder may have occurred in many parts of the world, for it might be confused with other diseases. If the disorder is nonfatal, clinical diagnosis may be impossible without the availability of skin and serological tests. In fatal cases the process may escape true pathological recognition, as happened for years in the case of the animal paralysis. Worms may be recognizable only in acute stages, and the lesion may be microscopic. Reference is made to literature on such entities as eosinophilic meningitis with a focal malacia, subacute degenerative softenings, and necrotizing myelitis, of which a possible nematodal cause might be considered.

The problems of (*a*) clinically inapparent, or masked, helminthic infection of the nervous system, (*b*) dual infection with virus and helminth, (*c*) migratory paths of the worm to the nervous system, and (*d*) the possibility of helminths being involved in the epidemiology of neurotropic virus infections are discussed.

54. Jaques, W. E.: Sarcoidosis: A Review and a Proposed Etiologic Concept, A. M. A. Arch. Path. **53**:558, 1952.

55. Beaver, P. C.; Snyder, C. H.; Carrera, G. M.; Dent, J. H., and Lafferty, J. W.: Chronic Eosinophilia Due to Visceral Larva Migrans: Report of 3 Cases, Pediatrics **9**:7, 1952.

EFFECTS OF ISOTONIC INTRAVENOUS SOLUTIONS ON NORMAL AND INCREASED INTRACRANIAL PRESSURE

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THE PRESSURE of the cerebrospinal fluid is dependent upon the volumes of blood, cerebrospinal fluid, extracellular fluid, and intracellular fluid within the cranial cavity. The alteration in cerebrospinal fluid pressure resulting from expansion of the extracellular fluid volume, as opposed to an expansion of the intracellular fluid volume, is of theoretical interest and may be of practical importance in the management of patients with increased intracranial pressure. The relative volumes of the extracellular and intracellular fluids can be experimentally changed by taking advantage of the different volumes of distribution of two isotonic solutions, 0.9% saline and 5% dextrose in water, following intravenous administration. The rapid intravenous administration of either solution causes an initial expansion of the plasma volume. The further distribution of 0.9% saline is essentially limited to the extracellular fluid volume, while 5% dextrose in water is distributed to both the extracellular and the intracellular fluid volume. Thus, saline may be considered to be distributed through about 20% of the body weight, while 5% dextrose in water is distributed through 65% of the body weight.[1]

There is considerable difference of opinion as to the effect of these isotonic solutions on the elevated intracranial pressure which may be associated with craniocerebral trauma and space-taking lesions. The administration of isotonic saline has been considered to increase the degree of "cerebral edema," and the strict limitation of salt during the first 48 hours after operation has been recommended.[2] On the contrary, Moyer and co-workers have stated that the intravenous administration of 5% dextrose in water increases the intracranial pressure and have

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1. (*a*) Peters, J. P.: Body Water: The Exchange of Fluids in Man, Springfield, Ill., Charles C Thomas, Publisher, 1935. (*b*) Wolf, A. V.: The Urinary Function of the Kidney, New York, Grune & Stratton, Inc., 1950.

2. Erickson, T. C., in Bancroft, F. W., and Pilcher, C., Editors: Surgical Treatment of the Nervous System: Cranial and Intracranial Surgery, Tumors, Epilepsy and Cranial Nerve Disorders, Spinal Cord, Autonomic Nervous System, Peripheral Nerves, Philadelphia, J. B. Lippincott Company, 1946. Matson, D. D.: Treatment of Acute Craniocerebral Injuries Due to Missiles, Springfield, Ill., Charles C Thomas, Publisher, 1948. Fine, J.: Care of the Surgical Patient, Including Pathologic Physiology and Principles of Diagnosis and Treatment, Philadelphia, W. B. Saunders Company, 1949. Davis, L.: The Principles of Neurological Surgery, Ed. 3, Philadelphia, Lea & Febiger, 1946.

advised that 5% dextrose in water should not be given during the course of intracranial operations, but that deficits of fluid volume should be replaced with isotonic salt solutions.[3]

The comparative effects of isotonic saline solution and isotonic dextrose solution in water on the intracranial pressure were therefore studied in normal dogs and in dogs with a sustained increase in intracranial pressure.

METHODS

Seventy-one experiments were performed on 31 female dogs anesthetized with intravenously administered sodium pentobarbital. Small additional doses of pentobarbital were given intraperitoneally during the experiment in order to maintain a stable corneal reflex and respiratory rate.

Cisternal, femoral arterial, and central venous pressures were measured with Statham strain gauges and continuously recorded on a Brush oscillograph. Central venous pressure was obtained by threading a polyethylene catheter into the superior vena cava. All pressures were referred to a point level with the midsternum as zero. The urine output was obtained by an indwelling catheter. Base-line pressures were recorded for 20 minutes before any infusion was begun.

Both normal dogs and dogs with a sustained increase in intracranial pressure were studied. The elevation in intracranial pressure was obtained by implantation under sterile conditions of about 6 gm. of bone wax [4] in the extradural space. The 1-cm. cranial defect was securely closed with dental cement.

Paired experiments were performed on the same dog, and the pressure changes following intravenous administration of an equal volume of either solution—isotonic saline or 5% dextrose in water—administered at intervals of at least two days, were noted. In seven experiments 5% dextrose in isotonic saline was also administered. After the initial pressures became stabilized, 5 to 50 cc. per kilogram of body weight was injected into the lateral saphenous vein over a five- to seven-minute period, and the pressures were recorded during the following two-hour period.

RESULTS

1. *Control Studies.*—Two dogs were studied for 2½ hours, receiving no fluid intravenously, in order that the variation in cerebrospinal fluid pressure, venous pressure, and arterial pressure might be noted under the influence of anesthesia alone. These pressures were strikingly constant, the variation in each instance being less than 10% of the initial pressure.

2. *Changes in Arterial and Venous Pressure.*—Central venous pressure was measured in all experiments, and arterial pressure, in 12 experiments. There were an acute elevation in venous pressure during the five-minute period of injection of either solution and a concomitant rise in cerebrospinal fluid pressure during this period only. The venous pressure fell rapidly to its initial level during the following three to five minutes and varied within 10% of this level during the rest of the two-hour period. The height of the venous pressure elevation was directly correlated with the volume of fluid injected and its speed of injection. The arterial pressure showed no such acute rise, although the pulse pressure frequently widened during the period of injection. There was a tendency for the mean arterial pressure

3. Wilson, B. J.; Jones, R. F.; Coleman, S. T., and Moyer, C. A.: Effects of Various Hypertonic Sodium Salt Solutions on Cisternal Pressure, Surgery **30**:361, 1951. Moyer, C. A.: Fluid Balance: A Clinical Manual, Chicago, The Year Book Publishers, Inc., 1952.

4. Equal parts of spermaceti and sesame oil, marketed by Ethicon Suture Laboratories, New Brunswick, N. J.

to increase gradually during the two-hour interval, which is attributable to the effect of pentobarbital anesthesia.[5] Except during the injection period, the variation in cerebrospinal fluid pressure was independent of either the venous or the arterial pressure. The time at which the maximum pressure occurred was variable, ranging from 35 to 100 minutes after the injection, both in normal dogs and in dogs with increased intracranial pressure. The results of a typical experiment illustrating these changes in a dog receiving 5% dextrose in water are presented in Figure 1. Similar venous pressure curves occurred in all experiments.

3. Comparative Effects of Isotonic Dextrose and Saline Solutions.— (a) Normal Dogs: Nineteen paired experiments were performed on 15 normal dogs,

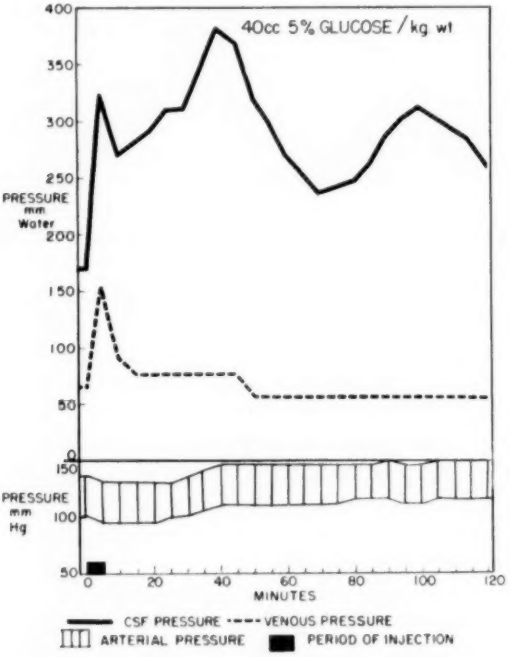

Fig. 1.—A typical experiment illustrating the correlation of the cerebrospinal fluid pressure and the venous pressure during the period of injection. Subsequently, the change in cerebrospinal fluid pressure is independent of the venous and arterial pressures.

each animal receiving from 5 to 50 cc. per kilogram of body weight of one solution, and the pressure responses were compared with those which followed administration of an equal volume of the other solution several days later.

There was a consistent difference in the responses of cerebrospinal fluid pressure to these two solutions. The cerebrospinal fluid pressure was elevated after the administration of either solution, but the response following the administration of

5. Corcoran, A. C., and Page, I. H.: Effects of Anesthetic Dosage of Pentobarbital Sodium on Renal Function and Blood Pressure in Dogs, Am. J. Physiol. **140**:234, 1943.

dextrose was consistently greater than that following the administration of saline. Figure 2 reveals the comparative response to these solutions in the same dog receiving four different volumes, 15, 25, 40, and 50 cc. per kilogram of weight, and illustrates the consistently greater response to dextrose, as well as the correlation of the magnitude of the response with the volume administered. Figure 3 *B2* reveals the average response in 19 such paired experiments performed on normal dogs receiving from 5 to 50 cc. per kilogram of either solution (average 25 cc. per kilogram of weight). The average elevation of pressure during the two-hour

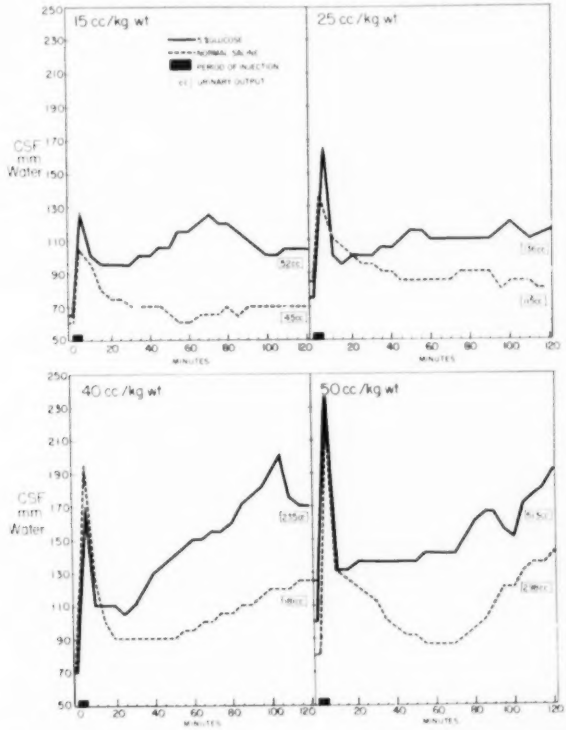

Fig. 2.—Changes in cerebrospinal fluid pressure in four paired experiments on one dog (weight, 11 kg.), illustrating the consistently greater pressure response and urinary flow following injection of 5% dextrose in water with four different doses.

period following the administration of dextrose was 147 mm. H_2O, 65% above the initial pressure, and the average elevation after the administration of saline was 117 mm. H_2O, 28% above the initial pressure. The greater the volume administered, the greater was the average pressure elevation; but in every experiment, at any given dose, the response to dextrose was about twice the response to saline.

The cerebrospinal fluid pressure remained elevated after the two-hour period with doses greater than 20 cc. per kilogram of body weight; longer recording revealed that the pressure fell to the initial level after most of the load had been

excreted in the urine, as late as five hours after injection. The urinary flow during the two-hour period following the administration of 5% dextrose in water was 5 to 50% greater than the flow after the administration of saline in all experiments.

(b) Dogs with Increased Intracranial Pressure: Paired experiments were performed on five dogs having sustained increases in cerebrospinal fluid pressure secondary to implantation of the extradural mass. Studies were performed three to seven days after operation, and the pressures following the administration of an equal volume, 7 to 40 cc. per kilogram of body weight, of either dextrose solution or saline, were recorded. The initial pressure varied from 160 to 310 mm. of water, the average being 200 mm. in the five experiments in which dextrose was given, and 211 mm. in the case of saline. Figure 3 *B1* reveals the pressure responses in

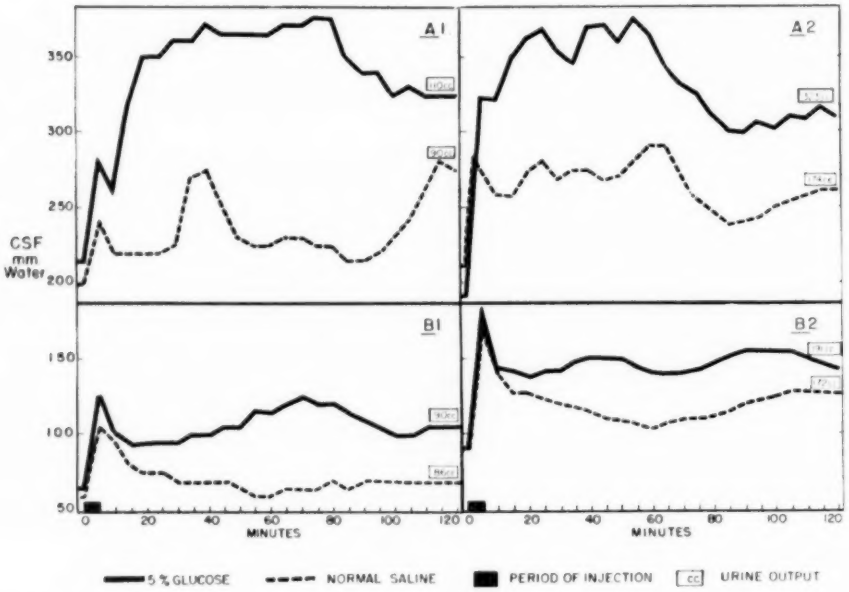

Fig. 3.—*A1*, comparative changes in cerebrospinal fluid pressure in a 13-kg. dog with increased intracranial pressure secondary to implantation of an extradural mass, after injection of 15 cc. per kilogram of 5% dextrose in water and of isotonic saline.

B1, pressure change prior to operation in the same dog studied in *A1*, receiving the same doses.

A2, average pressure change in five dogs studied after operation, receiving both solutions, with an average dose of 29 cc. per kilogram of body weight.

B2, average pressure change in 19 normal dogs, receiving both solutions with an average dose of 25 cc. per kilogram of body weight.

a normal dog (weighing 16 kg.) receiving an equal volume of the two solutions, 15 cc. per kilogram of weight. The average pressure after dextrose administration was 124 mm. H_2O, 54% above the initial pressure, and after saline administration, 75 mm. H_2O, 36% above the initial pressure. Figure 3 *A1* shows the pressure responses in the same dog as that referred to in Figure 3 *B1* when studied post-operatively and given the same dose. The average pressure after dextrose was

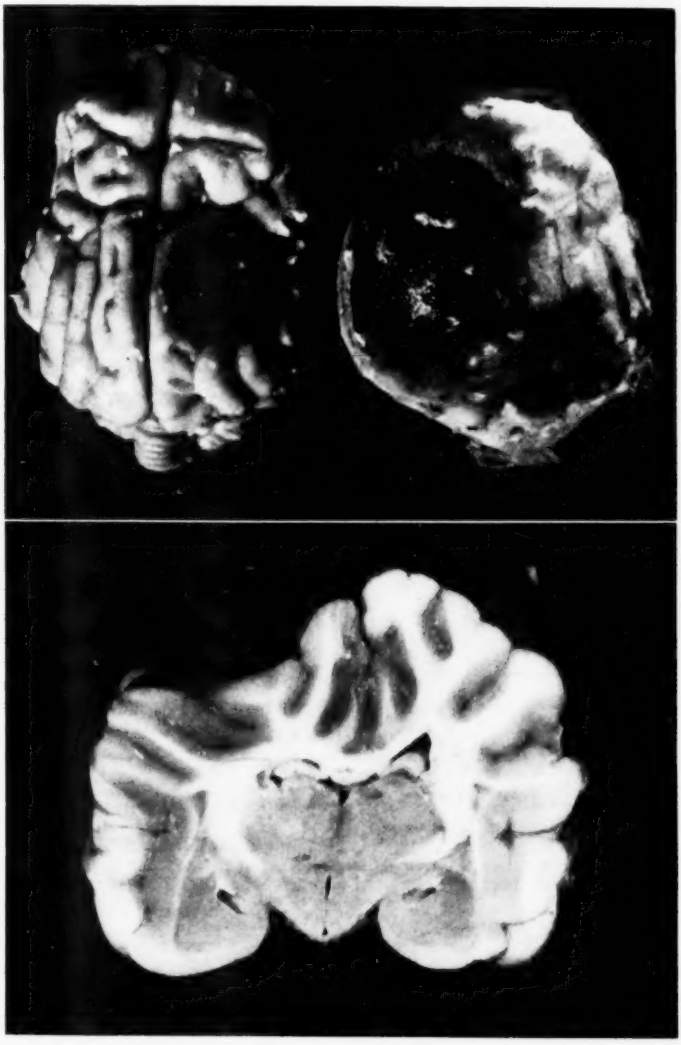

Fig. 4.—Postmortem material from a dog, obtained three months after operation, demonstrating the extradural mass fixed to the inner surface of the calvaria and displacement and compression of the right hemisphere. The pressure changes in this dog are charted in *A1* and *B1* of Figure 3.

344 mm. H_2O, 60% above the initial pressure, and after saline it was 240 mm. H_2O, 25% above the initial pressure. In each of the five dogs studied in this manner the response to dextrose was about twice that to saline. Figure 3 *A2* illustrates the average pressure curve for the five experiments. The average pressure over the two-hour period after administration of dextrose was 334 mm., 67% above the initial pressure, and after saline, 264 mm., 25% above the initial pressure.

About 12 days after operation the initial pressure fell toward normal levels. Postmortem examination revealed the mass to be rigidly fixed to the calvaria, sealing the cranial burr hole. The dura was intact and not adherent to the underlying cortex. The hemisphere was depressed by the mass and displaced toward the opposite side. The ventricular system was compressed but not obstructed.

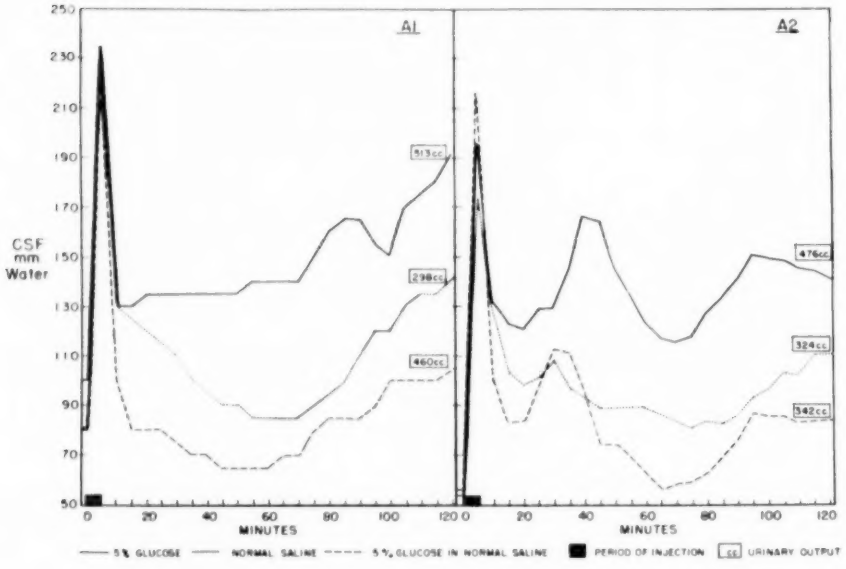

Fig. 5.—*A1*, typical experiment illustrating the comparative changes in cerebrospinal fluid pressure following injection of the three solutions (50 cc. per kilogram of body weight). *A2*, average changes in cerebrospinal fluid pressure in seven dogs studied in the same manner.

Figure 4 (*A* and *B*) illustrates the typical findings in a dog killed three months after operation.

4. *Comparative Effects of 5% Dextrose in Isotonic Saline, Isotonic Saline, and 5% Dextrose in Water.*—In view of the difference in responses to 5% dextrose in water and to isotonic saline, additional experiments were performed to study the cerebrospinal fluid pressure response to 5% dextrose in isotonic saline. Seven normal dogs were studied after the administration of 50 cc. per kilogram of body weight of each solution at intervals of several days. Figure 5 *A1* shows the pressure curves for one dog, and Figure 5 *A2*, the average pressure responses to the three solutions in the seven dogs studied. The average pressure after 5% dextrose in water was 188 mm. H_2O, 77% above the initial pressure; after isotonic saline,

148 mm. H_2O, 44% above the initial pressure, and after 5% dextrose in isotonic saline, 137 mm. H_2O, 34% above the initial pressure. In all cases the response to 5% dextrose in saline approximated the response to saline alone. Statistical analysis using Fisher's t test [6] revealed a high degree of significance for the response to dextrose in water as compared with that to the other solutions ($P > 0.001$), but no significant difference between the response to isotonic saline and 5% dextrose in saline ($P > 0.2$).

COMMENT

The greater increase in the intracranial pressure following the administration of 5% dextrose in water than that following administration of an equal volume of isotonic saline may be explained by the distribution of these fluids after injection. The well-known effects of hypertonic solutions and hypotonic solutions or distilled water on the cerebrospinal fluid pressure demonstrate that the relative volumes of the intracellular fluid, interstitial fluid, and cerebrospinal fluid, which are altered by the osmotic gradients established by such solutions, are of major importance in determining the level of the cerebrospinal fluid pressure.[7] However, 5% dextrose in water and isotonic saline are both isotonic fluids, and therefore the cerebrospinal pressure changes noted in the present experiment are not due to such osmotic gradients but are related to the distribution of the water of these solutions in the body-water compartments. Figure 6 illustrates the presumed distribution of these solutions through the body-water compartments. The distribution of 0.9% saline is essentially limited to the extracellular fluid because of the relative impenetrability of sodium into cells, and the distribution of the water of 5% dextrose solution includes both the extracellular and the intracellular fluid because of the ready penetration of this solution into cells.[8] Although these observations apply to the body as a whole, the water exchange of the brain behaves in a similar fashion [9]; i. e., deuterium oxide (heavy water) rapidly penetrates the brain tissue from the plasma (half-time for equilibrium being three minutes)[9], while the rate of radioactive sodium equilibrium between plasma and brain is much slower (equilibrium not taking place for 62 hours).[10] The average cerebrospinal fluid pressure response to 5% dextrose in water was twice as great as that to administration of an equal volume of saline, demonstrating that the level of the cerebrospinal fluid pressure is influenced more by systemic expansion of the volume of the total body water (extracellular and intracellular fluid) than by an expansion limited to the extracellular fluid.

Possible alteration in the volume of the cerebrospinal fluid induced by these solutions must also be considered in any explanation of the differing pressure responses noted. Unfortunately, there is no reliable method for measuring the volume of cerebrospinal fluid under these conditions. However, the difference in

6. Fisher, R. A.: Statistical Methods for Research Workers, London, Oliver & Boyd, Ltd., 1938, p. 128.

7. Weed, L. H., and McKibben, P.: Pressure Changes in the Cerebro-Spinal Fluid Following Intravenous Injection of Solutions of Various Concentrations, Am. J. Physiol. **48**:512, 1919.

8. Krogh, A.: Active and Passive Exchanges of Inorganic Ions Through the Surfaces of Living Cells and Through Living Membranes Generally, Proc. Roy. Soc., London, s.B. **133**:140, 1946.

9. Bering, E. A., Jr.: Water Exchange of Central Nervous System and Cerebrospinal Fluid, J. Neurosurg. **9**:275, 1952.

10. Hahn, L., and Hevesy, G.: Rate of Penetration of Ions Through the Capillary Wall, Acta physiol. scandinav. **1**:347, 1941.

time necessary for equilibration between the cerebrospinal fluid and plasma for deuterium oxide (heavy water) and radioactive sodium (Na^{24}), administered intravenously, is very striking. In the dog, the time necessary for the deuterium in the cisternal cerebrospinal fluid to reach one-half the serum concentration is about 20 seconds.[9] The equilibration time for tagged sodium is much slower, final equilibration not taking place in the cerebrospinal fluid for as long as 21 hours after intravenous injection.[11] The effects of 5% dextrose in water and isotonic saline on the cerebrospinal fluid pressure reflect this ready equilibration of administered water with the cerebrospinal fluid and the slow penetration of sodium into the cerebrospinal fluid.

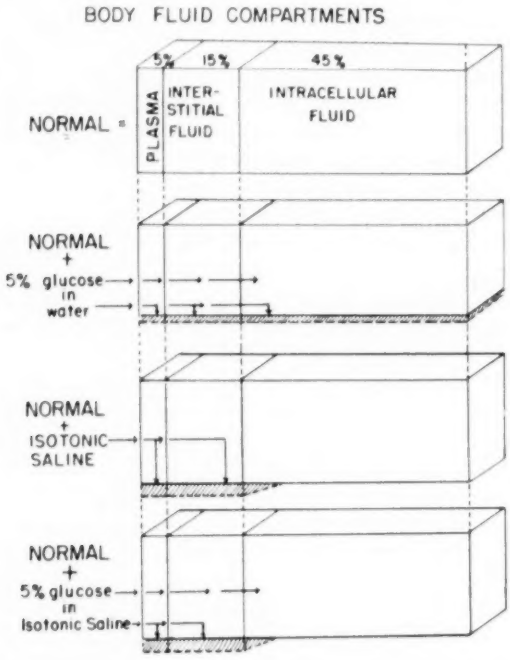

Fig. 6.—Diagram illustrating the distortion in the body-fluid compartments which theoretically occurs with introduction of these solutions into the plasma. Modified from Wolf.[1b]

Whether the greater pressure response following 5% dextrose in water is a reflection of an increase in cellular volume or an increase in cerebrospinal fluid volume is uncertain. Probably an increase in both volumes, as well as some increase in the extracellular fluid volume, results in the rise in pressure which follows the administration of 5% dextrose in water. The rise in pressure following the administration of saline is largely due to an expansion of the extracellular fluid volume alone.

11. Greenberg, D. M.; Aird, R. B.; Boelter, M.; Campbell, W; Cohn, W., and Murayama, M.: Study with Radioactive Isotopes of the Permeability of the Blood-Cerebrospinal Fluid Barrier to Ions, Am. J. Physiol. **140**:47, 1943.

It should be noted that the urinary flow following the administration of 5% dextrose in water is from 5 to 50% greater than the flow after the administration of saline. The more rapid excretion of the fluid load tends to diminish the magnitude of the body-water expansion following the administration of 5% dextrose in water. This suggests that had the animals been anuric the pressure response to dextrose would have been even greater than that noted.

In view of the frequent need for giving carbohydrates parenterally in the presence of increased intracranial pressure, the effects of 5% dextrose in saline were compared with those induced by equal volumes of isotonic saline and 5% dextrose in water. Although 5% dextrose in saline is a slightly hypertonic solution, the distribution of this solution is essentially the same as the distribution of isotonic saline alone, in that the water of the solution is held in the extracellular fluid volume by the presence of sodium, while the dextrose is utilized, with little change in intracellular volume occurring. The cerebrospinal fluid pressure curves following administration of these solutions reveal a consistent similarity between the effects of 5% dextrose in saline and of isotonic saline, as opposed to the twofold magnitude of the response to 5% dextrose in water. Indeed, the pressure change following administration of 5% dextrose in saline tended even to be slightly less than the pressure change after isotonic saline; although this difference was not statistically significant ($P > 0.2$), it might be a result of the slight hypertonicity of 5% dextrose in saline.

In these experiments large volumes were injected over a five-minute period in order to increase the magnitude of response and better to control the experimental conditions. One must, therefore, be cautious in applying such experimental data to clinical situations. In two patients with normal intracranial pressures, several months after severe head injury, infusion of 1,500 cc. of either 5% dextrose in water or isotonic saline over a 60- to 90-minute period did not affect the cerebrospinal fluid pressure at all.[12] By analogy with the results obtained in dogs with increased intracranial pressure, it might be expected, however, that patients with increased intracranial pressure would also show a greater response to the administration of 5% dextrose in water than that following administration of an equal volume of isotonic saline.

The frequently stated clinical dictum that salt restriction is indicated in the management of patients with increased intracranial pressure due to a space-taking lesion or "cerebral edema,"[2] is largely based on an analogy to the benefits of salt restriction in patients with generalized edema due to congestive heart failure. However, these experiments demonstrate that the intracranial pressure is increased to a greater extent by hydration with a salt-free solution than with isotonic saline. It is suggested that the administration of isotonic saline or 5% dextrose in saline to critically ill patients with elevated intracranial pressure is less hazardous than the administration of 5% dextrose in water. This conclusion is in agreement with that of Moyer,[3] that 5% dextrose in water should not be given intravenously during the course of intracranial operations. While patients requiring parenteral administration of fluids should not be overloaded with salt, the potential hazards of intravenous hydration with salt-free solutions should be recognized.

12. Fishman, R. A., and Fowler, E.: Unpublished data.

SUMMARY

The change in cerebrospinal fluid pressure following intravenous administration of 5% dextrose in water is compared with that following infusion of isotonic saline in normal dogs and in dogs with a sustained increase in cerebrospinal fluid pressure secondary to the implantation of an extradural mass. For any given volume of fluid administered (5 to 50 cc. per kilogram of body weight), the increase in cerebrospinal fluid pressure following administration of 5% dextrose in water was about twice that following administration of an equal volume of isotonic saline. The cerebrospinal fluid pressure response following the administration of 5% dextrose in saline was essentially the same as the response to isotonic saline alone.

The difference in response to these isotonic fluids may be explained by the distortion induced in the volumes of the body-fluid compartments and the cerebrospinal fluid volume. The water of 5% dextrose is distributed throughout the intracellular fluid and extracellular fluid volumes, and is in ready equilibrium with the cerebrospinal fluid. The distribution of isotonic saline is limited to the extracellular fluid, and the penetration of sodium into the cerebrospinal fluid takes place slowly.

The administration of 5% dextrose in water to patients with increased intracranial pressure would seem to be more hazardous, in terms of the greater elevation in cerebrospinal fluid pressure that may result, than the administration of an equal volume of isotonic saline.

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EFFECTS OF INTENSIVE PSYCHOTHERAPY ON EPILEPTIC CHILDREN

Report on Three Children with Idiopathic Epilepsy

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THE PSYCHIATRIC study of genuine epilepsy has produced information which strongly suggests that psychologic factors play a role in the elaboration or exacerbation of epileptic phenomena. The literature on psychopathology of epilepsy has been thoroughly reviewed elsewhere.[1] Various studies, mostly clinical, have led to the development and elaboration of hypotheses concerning the psychobiological functions of both the aura [2] and the seizure manifestations.[3]

If psychopathological hypotheses of the origin of the epileptic syndrome have some basis in fact, there should be a possibility through psychologic means of modifying the frequency and/or form of the seizures in certain epileptic patients. The neurophysiological correlates of epileptogenic phenomena, such as the electroenceph-

From the Institute for Psychosomatic and Psychiatric Research and Training, Michael Reese Hospital and the National Institute of Mental Health, Public Health Service, United States Department of Health, Education, and Welfare, Bethesda, Md.

1. (*a*) Mittelman, B.: Psychopathology of Epilepsy, in Epilepsy: Psychiatric Aspects of Convulsive Disorders, edited by P. H. Hoch and R. P. Knight, New York, Grune & Stratton, Inc., 1947. (*b*) Schick, A.: A Contribution to the Psychopathology of Genuine Epilepsy, Psychoanalyt. Rev. **36**:217, 1949.

2. Hendrick, I.: Psychoanalytic Observations on the Aura of 2 Cases with Convulsions, Psychosom. Med. **2**:43, 1940. Lennox, W. G., and Cobb, S.: Epilepsy: Aura in Epilepsy: A Statistical Review of 1,359 Cases, Arch. Neurol. & Psychiat. **30**:374, 1933.

3. (*a*) Barker, W.: Studies on Epilepsy: The Petit Mal Attack as a Response Within the Central Nervous System to Distress in Organism-Environment Integration, Psychosom. Med. **10**:73, 1948. (*b*) Bartemeier, L. H.: Concerning the Psychogenesis of Convulsive Disorders, Psychoanalyt. Quart. **12**:330, 1943. (*c*) Clark, L. P.: The Psychobiologic Concept of Epilepsy, A. Res. Nerv. & Ment. Dis., Proc. **7**:65, 1931; (*d*) Clinical Studies in Epilepsy, Utica, N. Y., State Hospitals Press, 1917; (*e*) A Study of Certain Aspects of Epilepsy Compared with the Emotional Life and Impulsive Movements of the Infant, Interstate M. J. **22**:969, 1915. (*f*) Cobb, S.: Borderlands of Psychiatry, Harvard Monographs in Medicine and Public Health, No. 4, Cambridge, Mass., Harvard University Press, 1944; (*g*) Psychiatric Approach to the Treatment of Epilepsy, Am. J. Psychiat. **96**:1009, 1940. (*h*) Greenson, R. R.: On Genuine Epilepsy, Psychoanalyt. Quart. **13**:139, 1944. (*i*) Heilbrunn, G.: Psychodynamic Aspects of Epilepsy, ibid. **19**:145, 1950. (*j*) Jelliffe, S. E., and White, W. A.: Diseases of the Nervous System: Text-Book of Neurology and Psychiatry, Ed. 6, Philadelphia, Lea & Febiger, 1935. (*k*) Jelliffe, S. E.: Dynamic Concepts of the Epileptic Attack, Am. J. Psychiat. **92**:565, 1935. (*l*) Kardiner, A.: The Bio-Analysis of the Epileptic Reaction, Psychoanalyt. Quart. **1**:375, 1932. (*m*) Menninger, K. A.: Psychoanalytic Study of a Case of Organic Epilepsy, Psychoanalyt. Rev. **13**:187, 1926. (*n*) Schilder, P.: Introduction to a Psychoanalytic Psychiatry, Nervous and Mental Disease Monograph, No. 50, New York, Nervous and Mental Disease Publishing Company, 1928.

alogram, may possibly also be modifiable through psychologic means. Barker and Barker [4] and others, for instance, have collected evidence that exploratory psychologic investigations may modify the cerebral bioelectric activity of known epileptic patients. They have interviewed epileptic subjects during electroencephalographic recordings and have reported that appropriate emotional stresses can lead to transitory electroencephalographic seizure discharges. Such observations have not been substantially confirmed.

PURPOSE OF THE INVESTIGATION

The present study was developed to test several relevant hypotheses.

1. Psychologic factors, as well as other factors, contribute to the form and frequency of the clinical manifestations of chronic idiopathic convulsive conditions in children.

2. Psychotherapy can modify the form and frequency of the convulsive manifestations of idiopathic epilepsy in children.

3. The form and frequency of the child's convulsive manifestations vary not only with the status of the child's intrapersonal neurotic conflicts but also with the status of the neurotic conflicts in key members of the family (or others).

SOURCES OF CASE MATERIAL AND GENERAL COMMENTS ON PROCEDURES

Epileptic children, instead of adults, were chosen as subjects, in the expectation that the children might have more potential for change in psychologic, behavioral, and physiological activity than have adults.

The three children participating in this study were referred for psychiatric evaluation to the Child Psychiatry Clinic, Michael Reese Hospital. The children were chosen primarily for two reasons: The diagnosis of "idiopathic epilepsy" had been established by careful neurological examinations, and the parents of the children were agreeable to cooperating in a psychotherapeutic program of indefinite duration. It is important to add that the psychiatric problems of these children did not appear, on superficial inspection, any more pronounced than those of other children with convulsive manifestations referred to the Clinic. Furthermore, they were the only three epileptic children whom I treated during the period of this study.

The type of therapy these children received may be categorized generally as "psychoanalytic psychotherapy." K. (Case 1) was seen most frequently, on the average of three to four times a week; N. (Case 2) and R. (Case 3) were seen once a week. Each child was seen for a total of more than 100 therapeutic sessions.

K. and N., boys 5 and 10 years of age respectively, were seen in a playroom setting by the therapist, the patients using the play materials only when they chose to do so. R., an adolescent boy, aged 17, was seen in an interviewing room for adults. He usually sat in a chair. Occasionally he lay on a couch, if he so desired.

One or both parents of each child were interviewed before psychotherapy of the children was started by the psychiatrist, and they were seen at subsequent intervals by the psychiatrist when indicated. The mothers of K., N., and R. and the father of N. were studied and treated collaboratively by psychiatric social workers.

Evaluation of the efficacy of a therapeutic agent, under any circumstances, is acknowledged to be a complicated and exacting procedure, requiring careful assessment of the criteria of improvement. Evaluation of psychotherapeutic effects, because of various subjective consider-

4. (*a*) Barker, W., and Barker, S.: Experimental Production of Human Convulsive Brain Potentials by Stress-Induced Effects upon Neutral Integrative Function: Dynamics of the Convulsive Reaction to Stress, A. Res. Nerv. & Ment. Dis., Proc. (1949) **29**:90, 1950. (*b*) Higgins, J.; Lederer, H., and Rosenbaum, M.: Life Situations, Emotions, and Idiopathic Epilepsy, ibid. **29**:137, 1950.

ations involved, is still in the process of being established on a reasonably objective, if not a quantitative, footing. The present study was an attempt to improve on previous evaluations of psychotherapeutic efforts in persons with epilepsy by including, besides a report on the clinical changes during and after treatment, the results of electroencephalographic studies and objective psychologic tests in the children who received intensive psychotherapy. In tabulation of the clinical changes, particular attention was paid to modifications in the frequency and form of epileptic seizures and other habitual behavior of the patient in reaction to stressful situations.

The advisability of suitable control studies was considered. One control arrangement might have been to study three or more comparable epileptic subjects not receiving formal psychotherapy but treated only according to a standard medical regimen. It was considered impossible, however, to match perfectly children receiving psychotherapy with other children in respect to variables that might be relevant and etiologically significant, e. g., sex, age at onset of epilepsy, type of seizures, type of electroencephalographic tracings, genetic background, sibship, child-parent relationships, and life experiences. It was felt that the only way of ascertaining that psychotherapy received by the epileptic children and/or their parents was of relevance in effecting clinical changes observed in the children was to use the three children as their own controls. Any evidence in a child of an increase in the seizure threshold could be considered a valid criterion of symptomatic improvement. Indicators of increase in the seizure threshold would be decrease in seizure frequency, decrease in the amount of anticonvulsant medication required, decrease in the ability of psychologic or other stress to precipitate seizures, and improvement in the electroencephalogram. The method of intraindividual controls was not regarded as a solution to the need for scientific rigorousness in assessing the effect of psychotherapy on a small group of subjects. Rather, it was thought to be a compromise until larger groups of subjects could be appropriately studied.

Electroencephalographic studies were done either at the Epilepsy Clinic, Illinois Neuropsychiatric Institute, or the Electroencephalography Laboratory, Michael Reese Hospital. Psychologic tests were administered at the Psychology Laboratory, Institute for Psychosomatic and Psychiatric Research and Training, Michael Reese Hospital.

The following case summaries will give for each patient the pertinent identifying data, frequency and duration of psychotherapeutic sessions, descriptive classifications of the seizures and personality disorder, known and presumptive pathogenic etiological factors in the epileptic syndrome, and reviews of the clinical manifestations, electroencephalographic patterns, and psychologic test findings before, during and after the period of psychotherapy.

SUMMARY OF CASES

CASE 1.—K., a boy born June 17, 1945, was started in psychotherapy in April, 1950, at the age of 4 years 10 months. He was seen four times a week for 60 hours and thereafter three times a week, for a total of 140 sessions. The therapy was terminated in June, 1951, because at the time he was considered to be in no further need of treatment.

The diagnostic categories which best describe his condition are (1) idiopathic epilepsy, with atypical and possible petit mal seizures, and (2) inhibited, infantile character disorder.

Clinical Manifestations Before Psychotherapy.—His typical ictal manifestations included (1) daily, generally nocturnal, sudden, explosive episodes of twitching and jerking of the hands, arms, and facial musculature, with or without loss of consciousness, and (2) frequent daily transient trance-like states, with brief periods of disturbance of consciousness. All these convulsive manifestations had their onset and development gradually between March and May, 1948, when K. was approaching the age of 3 years.

He had certain other patterns of behavior not demonstrated to be of ictal nature. These included nocturnal, and occasional diurnal, enuresis; night terrors; temper tantrums; inarticulate, and frequently unintelligible, speech with occasional stuttering; avoidance of, or hostile activity toward, other children; negativism; feeding difficulty (recalcitrance to eating as much food as his mother wished), and general retardation in learning.

Possible Pathogenic Factors in the Epileptic Syndrome.—There was no familial history of epilepsy or relevant history of trauma or infection of the central nervous system. All neurological examinations had revealed nothing significant. An electroencephalographic report at the age of 4 years 2 months noted a spike seizure focus in the left temporal area. The birth and infantile development were normal, as determined from the hospital and well-baby clinic records. The mother personally reported, however, that he had been a particularly feeble nursling, showing little inclination to suckle on either the breast or the bottle as long or as vigorously as she thought he should. He walked at 9 months, vocalized before that, but did not begin to verbalize intelligibly until nearly 3 years of age.

The onset of changes in K.'s personality occurred abruptly in March, 1948, when he was approaching 3 years of age. Previously a very docile, passive child, he began to be rebellious, negativistic, and demanding of indulgences. Coincident with these behavioral changes ictal manifestations appeared. This abrupt change in his characteristic behavior occurred while the mother was trying to effect a sudden change in her manner of handling him—from anxious overprotection to forceful insistence on his developing independence and self-reliance in isolated areas. For instance, she had begun making him walk to the store on his own, instead of always carrying him.

In May, 1948, he had a short bout of chickenpox, followed by aggravation of his irritable and negativistic behavior and ictal manifestations. Further aggravation of his personality and ictal disorder occurred after a tonsillectomy and adenoidectomy in October, 1948, surgical operations which the parents had secured on advice from a physician that they would remedy the child's "nervousness."

Collaborative psychiatric studies of the mother by a social worker indicated that, although a capable and maternal woman, the mother had been obsessed from K.'s birth with the irrational fear that he was a weakling and that he was destined to die in infancy. In consequence of this fear, she infantilized him considerably. He was still occasionally having a bedtime bottle at the time of his beginning psychologic treatment. On the other hand, though the mother was overprotective for fear he might be injured, she was also fearful he might hurt, or even kill someone if allowed freedom to express himself. She therefore restricted his more vigorous neuromuscular activities, e. g., crawling, climbing, and running in and out of the house, and personally supervised all his outside play activities and interactions with other children. In contrast to these special attitudes and feelings she had about K., she volunteered freely that she had had no such problems in nursing and rearing the patient's only sibling, a sister three years older than he. The mother revealed that sometimes she reacted toward K. as though he were one of her younger male siblings, whom she had had to accept the responsibility of rearing after the untimely death of her own mother, when she was 12. She also reacted to K. at times as though she were dealing with her father, who had been harsh, impetuous, and demanding. One memory that for her was particularly associated with feelings of humiliation and of rebellion toward males was that her father habitually had her wash his feet when he returned from work. A situation which mobilized and reinforced latent doubts she had about how safe a mother she was for a boy was the fact that her first pregnancy had terminated in the miscarriage of a male fetus.

The patient's father was a laborer in a steel factory. Though considered a reliable provider and conscientious family man, he took only passing interest in his son. He spent all his free time with cronies at work or in the company of his own father, toward whom he had a strong dependent attachment.

Effect of Anticonvulsant Medication Before the Start of Psychotherapy.—K. was taken to the Epilepsy Clinic, Illinois Neuropsychiatric Institute, in August, 1949, and the anticonvulsant medication was started—diphenylhydantoin (Dilantin) sodium 0.03 gm. four times a day, and phenobarbital, 0.03 gm. three times a day. His seizure manifestations persisted but in definitely milder form. His behavior disorder continued essentially unchanged or worsened.

Changes in Clinical Manifestations During and After Psychotherapy.—The first interview with K., in April, 1950, revealed that he was short for his age but of about average physique. His face appeared pale, and he bore an air of grim preoccupation, lacking completely any animation. His initial investigatory activity of the playroom and its contents was cautious and circumscribed. Verbalization was either absent or restricted to brief remarks. He indicated

either by gestures or by expectant waiting his apparent interest in some toys, e. g., blocks or an automobile. He would not use any such toys at first unless the therapist used them with him or nonverbally indicated it was acceptable for him to do so by himself.

It became clear in the early playroom sessions that many bodily movements, such as speaking, eating, or excreting, were associated with ideas of hurting or being hurt, and that the performance of such activities was interfered with because of the fear of retaliation and loss of security. As he began to learn in the treatment situation, essentially nonverbally, that he was not in danger and that the activities and ideas generated by him were not dangerous, he began to talk more and to express himself in play more freely.

Then, in his play, and increasingly in his vocalization and verbalization, he demonstrated a wish to be big, strong, and powerful. This trend was associated with his expressing fearful ideas that he might be too powerful—that he might hurt those on whom he depended for support and indulgence. He became interested in a toy drum and by gestures and looks indicated he wanted to pound on it, but he would not venture to do so at first. When he was satisfied that the therapist had a permissive attitude toward this striving, he chose to strike the drum gently with matchsticks rather than with the much heavier regular drumsticks, which were available. Even then, K. quailed at the little noise he personally originated. A moment later he smiled, then chuckled anxiously at the discovery that no dire consequences resulted. His boldness grew, and he spent periods building with blocks a small tower alongside a much taller tower. Invariably, when the tall tower got knocked down, accidentally or not, he knocked over the small tower purposely. With this type of play, the content of his growing verbal communications dealt with the relative sizes of objects, big and little, and their relative utility and advantages. Eventually, when even bolder, the scope of his playroom activities included periodic experimentation with a dart-shooting toy pistol. He then showed another pattern of activity: He would exhibit various kinds of trick shooting and gun play, punctuated with shouts of glee, and would then suddenly manifest signs of tension, peer around anxiously, and abruptly terminate and avoid this sort of play for a while. On one such occasion, when he had been merrily holding the gun behind him and shooting the dart forward between his legs and the state of tension and avoidance had suddenly ensued, he was asked why he was afraid of something when he seemed to find it fun to learn how to use parts of his body. He shook his head fearfully and stated frankly he did not know. Soon after this episode, while playfully lying prone on a table in the room and talking about a water-pistol fight he had had with a playmate, he began to move his hips in a coital manner while holding his hands together in a peculiar fashion in front of him to indicate they were not involved in this performance. When no remarks were made about this activity, he suddenly asked to go to the toilet to urinate. On returning to the playroom, he hastily reported spontaneously that he only touched his penis when he had to urinate. Later, his conflicting association of genitourinary activities with ideas of injuring someone or being injured came to the fore.

In the working through of the conflict of expressing various activities and self-imposed, autonomous inhibitions against talking about or carrying out such activities, some compromise solutions appeared. About this time, for a brief period, he made a furious effort to avoid coming to further psychotherapeutic sessions. This occurred because of a terrible fear that he might lose the security of parents or their surrogates if he continued to express inhibited wishes so freely. His wish to withdraw from treatment and his feeling of insecurity were altered by the therapist's indicating to him that his mother and father approved of his telling the therapist about his worries and by reminding him that his mother was seeing someone at the Clinic for her worries, too.

A two- to three-month period occurred during which he manifested transient muscular jerks and facial grimaces in the playroom (possibly partial duplications of the seizures he had had at home). These manifestations gave way to a period of hand washing, which was actually the most prolonged deviant motor expression observed. It cannot be proved that these motor acts—muscular twitches, grimaces, and hand-washing activity—constituted either alternate modes of discharging pent-up and conflictual tensions or epileptiform activity. It can be stated with certainty, however, that one mode of such habitual motor activity was superseded by another and that one or the other invariably preceded the verbalization of some new idea, fantasy, or feeling or followed the performing of some new, increasingly skilled, and organized pattern of behavior. For example, muscular twitches and facial grimaces appeared immediately

after he formlessly smeared with paint or cut with scissors for the first time. These movements suddenly reappeared later, immediately after he painted or cut out his first formed and structured productions.

His speaking habits also underwent modifications during the period of observation. After verbal communication became a regular accompaniment of other playroom activities, he would have sudden periods (sometimes lasting for several sessions) of relative muteness, always after some psychologic stress at home or in the playroom. His relative silence usually heralded the introduction of new psychologic material, and this was often communicated first in nonverbal activities and play. When he was not mute, interferences in the smooth, coordinated flow of verbalization, such as stuttering, were observed during periods when the expression of a strong emotion, usually anger, was for some reason or other blocked. When the therapist dealt with the unexpressed emotion openly, for example, by indicating acceptance of its expression or by exposing its irrational origin, the stuttering was regularly alleviated or eliminated completely.

K.'s testing out of his fantasies of great power and awful danger to others who frustrated him became a more and more integrated process. Instead of reacting to the termination of a therapeutic session or the realization that the therapist saw other children by making, for example, a clay ball and chewing it up and spitting it out, he accepted these realities without such primitive signs of distress. Frustrating situations of a more mature sort he then verbalized in terms of wanting to take the place of his father, who slept next his mother, or, again, in his own words, "Why can't I marry my mother and have her for myself?" He acted out these situations in the playroom in the form of rivalry with me. For instance, he climbed up on the playroom table and laughed and said that now he was much taller than the therapist and that the therapist had to do what he wanted. Later, showing increased ability to delay immediate satisfaction of wishes, he remarked during his play that in time he would really grow as tall as, or taller than, the therapist. Subsequent modifications of these fantasies of growing up included his often-expressed desire to have a horse to ride as big as "Hopalong Cassidy's." Eventually, and over a period of time, he began asking for information about processes such as childbirth and procreation, and these questions were subsequently elaborated, discussed, and worked through.

During the course of treatment there was seen a gradual, but certain, alteration in the frequency and form of his ictal manifestations and behavioral disorders, the changes coinciding in time with particular aspects of his treatment. At first, nocturnal epileptiform seizures were occurring almost nightly during the first 15 minutes of going to sleep; they consisted of incoordinate muscle jerkings, often preceded by a yell. The duration of these phenomena decreased to a few minutes and, finally, to momentary, mild to insignificant twitches of an arm, a leg, a finger, or a toe while he was falling asleep. At this point, after 1½ to 2 months of psychotherapy, night terrors became infrequent and nocturnal enuresis stopped. K. then showed a tendency to want to hug and kiss his mother. Soon after this period, however, he had transient recurrences of nocturnal fits and increases in diurnal temper tantrums, which appeared whenever his mother frustrated him in some receptive demand. On one occasion his mother weaned him completely from the bottle, and on another occasion she took toys away from him and returned them to children from whom K. had forcefully acquired them; on occasions of this sort, K. kicked, screamed, and bit at his mother. These reactions quieted after a time, aided undoubtedly by the mother's less anxious management of the boy. Then a new series of temper tantrums, this time without nocturnal jerkings, occurred coincidentally with his dealing with sibling rivalry situations in the playroom setting. During this series of temper outbursts he threw rocks at a boy and scratched his sister. On still another occasion, after asking his mother to let him sit on her lap, he scratched, bit, and spit at her soon after sitting there, without apparent provocation so far as the mother knew. This series of temper outbursts culminated in a single recurrence of a prolonged nocturnal grand mal seizure—the last during the period of psychotherapy. The latter shower of temper tantrums and the prolonged nocturnal grand mal seizure occurred at a time when the mother was presenting material to her social service therapist about her fears that she would hurt or injure the patient as she had feared she might hurt her younger male siblings. The mother was discussing also at this time a recurring, frightening dream of hers about a strange, vicious man who enucleated a little boy's eyes. This dream was presented by the mother to the social worker when the mother was discussing her strong feeling of urgent need to protect helpless children against potential physical harm.

An indication of K.'s increase in frustration tolerance and seizure threshold is afforded by an example of a situation occurring during the latter part of psychotherapy. K. had told his mother spontaneously that he did not want to grow up to be a big boy, and therefore he argued he should be allowed to sleep with her in the place of his father. He kept asking her whether she did not have a penis, too. When the mother frankly answered his questions about her genital apparatus and refused to have him sleep with her instead of the father, he became briefly furious and called her a "dirty rat." But with this predominantly verbal temper flash, his reactions of anger subsided. No seizure occurred. Shortly thereafter he evidenced no further protestations about the matter and expressed affectionate feelings toward her. Previously, the frustration associated with such an attempt at problem solving might have been followed by an epileptic seizure.

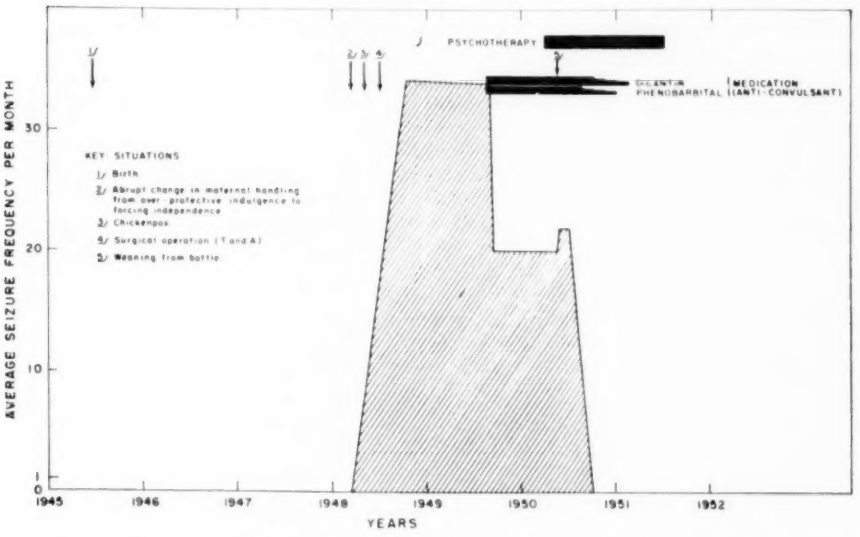

Chart 1 (Case 1).—Diagram summarizing the temporal relations of therapeutic events to average seizure frequency.

Summary: After 140 analytic treatment sessions, over a period of 14 months, the clinical changes which occurred may be enumerated as follows:

1. Psychologic treatment began April, 1950 (Chart 1). No further seizures occurred after September, 1950; and with the gradual withdrawal of all anticonvulsant medication during February and March, 1951, there was no recurrence of epileptic seizures. The seizure-free period at the time of this report has been longer than two years.

2. Enuresis and night terrors stopped. Play and social relations with other children improved. Normal investigative activity and success in the development of manual and intellectual skills occurred. School adjustment in kindergarten and first grade was moderately above average, intellectually and socially. Feeding difficulties no longer persisted.

3. There was no further stuttering, and speech was much more articulate and intelligible. Some fluctuating, mild speech disturbance persisted, consisting essentially in a tendency to mispronounce certain consonants. The latter was improving gradually.[5]

5. In the opinion of Dr. Joseph Wepman, a speech diagnostician and therapist, who examined the patient after the termination of psychotherapy, the speech diagnosis was "dysalia due to faulty auditory discrimination and lack of development." It was his prognosis that "the speech will become fairly adequate within two years with no teaching or formal training."

Psychodynamic Formulation of K.'s Personality Disorder.—K. had an infantile receptive, demanding orientation toward people, developed as a protection against the idea that he might be injured expressing independence and vigorous assertiveness or injure a source of security, such as the mother. This orientation was, furthermore a means of insuring himself of a continual supply of parental, particularly maternal, support, protection, and tenderness. There resulted an inhibition of the usual learning activities, effective aggression, speech development, and sphincter control. The advantage of such an orientation was the obtaining of some support, protection, and indulgence from the mother. The disadvantage was that the expected indulgences and infantilization could not be forthcoming from the mother forever.

K.'s interpersonal relations with his parents were found to contribute significantly to his intrapersonal conflict and his overt behavior patterns. The mother's hostile, depreciatory fantasies toward K. and her defensive restriction and overprotection of him were, indeed, a realistic basis for his fears that any of his feelings or actions might be harmful. The father's preference for the role of a son rather than the role of a father afforded K. limited avail from this parent.

The treatment procedure provided evidence that K. was especially vulnerable to frustrations in receiving continued infantile support and indulgence from the mother and to the restrictions by the mother in his experimental and investigatory activities. Such frustrations eventuated in explosive attacks of impotent rage, directed outwardly and toward himself, and/or convulsive seizures. These formulations appeared to be correlated with the incidence of the epileptic spells, the behavior maladjustments, and some of the retarded developmental characteristics of this boy.

Psychologic Tests.—Stanford-Binet Scale Form L: The results are tabulated.

	Feb. 15, 1949 (Before Psychotherapy)	Aug. 15, 1951 (After Psychotherapy)
Chronological age	4 yr. 8 mo.	6 yr. 2 mo.
Mental age	4 yr. 8 mo.	6 yr. 4 mo.
Intelligence quotient	100	103
Basal	Year 4	Year 6
Highest successes	Year 6	Year 7

Electroencephalographic Report.—1. Before Psychotherapy (August, 1949; age, 4 years 2 months): "The record reveals 6- to 7-cps activity in all leads, with constant spike seizure activity in the left temporal region, spreading to the left parietal area. The sleep record also shows the spiking in this area. The impression is that of a spike seizure focus in the left temporal area, spreading to the left parietal area." (F. A. Gibbs)

2. Before Psychotherapy (April, 1950; age, 4 years 10 months): "The record shows 8- to 9-cps activity in all leads, with frequent spike seizure discharges in the left parietal area, spreading to the left temporofrontal area during secobarbital-induced sleep. The impression is that of a spike seizure focus in the left parietal area." (F. A. Gibbs)

3. After Psychotherapy (April, 1951; age, 5 years 10 months): "The record shows 8- to 10-cps activity in all leads. There is no focus of abnormality and no seizure discharges. Sleep activity is normal. The impression is that of a normal electroencephalogram, both during waking and during sleep. The record shows great improvement over the two previous records." (F. A. Gibbs)

Rorschach Test (Dr. Samuel J. Beck).—Only one Rorschach test was made on this boy, two months after psychotherapy was terminated. It indicated that the child reacts to his unacceptable impulses with anxiety and a rigid pattern of defense. He is vulnerable to emotionally toned, exciting stimuli. He reacts to such stimuli with withdrawal—at one extreme to the level of complete blocking (one of his full rejections of a card). He also reacts to these stimuli with unstable, but not explosive, behavior however, in the form of some concretistic, immature thinking, immature language, and self-evaluative attitude. That the personality structure is at the level of neurosis is attested by a 'color-shock pattern.'

"Anxiety is mobilized in relation to the 'father' figure, to which he responds, 'looks like a giant, looks bad,' and also to the 'mother' figure, although not so severely. A confusion of the concept of man and woman occurs twice.

"His problem of mastering uncontrolled impulses is complicated by his relative lack of creative resources and his overly rigid pattern of inhibitions."

CASE 2.—N., a 10½-year-old boy with epilepsy, born Sept. 18, 1938, was treated psychotherapeutically from March, 1949, to June, 1951. He was seen regularly once a week for a total of a little more than 100 therapeutic sessions. The treatment was terminated, not because psychotherapy was considered completed but because the therapist had to leave the city for military service.

The diagnostic categories which roughly describe N.'s pathological condition include (1) idiopathic epilepsy with frequent daily "psychic or atypical" seizures, occasional psychomotor fits, and very rare grand mal seizures, and (2) a hysterical character disorder.

Clinical Manifestations Before Psychotherapy.—His ictal manifestations included psychic, atypical fits, precipitated usually only by looking through an ordinary window screen, or occasionally by looking at checkered or striped patterns on clothes, tablecloths, etc. (These seizures will henceforth be designated as "screen spells.") These fits consisted of spells of staring through the screen and were accompanied by uncoordinated, generally symmetrical shaking of the upper extremities. According to the parents, the arm movements looked to them like a bird's flapping its wings. Sometimes the arm movements, with accompanying head and neck motions, suggested to the parents protective or warding off actions against some threat to the child's head and neck. These seizures lasted from 1 to 45 minutes. N. would generally remain standing, would only rarely fall or bite his tongue, could not be communicated with during the spell, and could not recall what he had been doing during the spell. These episodes had had their onset in November, 1943, when he was 5 years of age, soon after the father had to leave home to enter active duty in the Army.

2. Psychomotor seizures, of recent origin, appeared at the age of 10 years. Typical in their pattern, lasting from 15 to 30 minutes, these were paroxysmal episodes of complicated and rather highly organized motor activity, with a prominent destructive component, e. g., tearing clothes to shreds or breaking furniture. He had no notion what led to these seizures and could not be communicated with during them. After the seizures he could not recall what he had done during them.

3. Grand mal seizures were rare. The first one had occurred at the age of 9 years, and one such seizure had occurred each year thereafter, accompanied by tonic and clonic phases and biting of the tongue on two occasions. The grand mal seizures all evolved during "screen spells."

Possible Pathogenic Factors in the Epileptic Syndrome.—There was no familial history of epilepsy or migraine and no relevant history of trauma or infection. His birth and development during infancy were free from known symptomatic disease. All neurological examinations revealed a normal state except for bilateral constriction of the peripheral visual fields ("tubular vision"), first appearing at the age of 10 years 4 months and lasting two months. Thorough neurological and ophthalmologic studies revealed a disturbance of the form fields, and not of the color fields, in this visual symptom, but no detectable structural or anatomical basis for it. The visual field defect cleared up soon after the advent of psychotherapy and did not recur. The first electroencephalographic recording, done when he was 6 years old, showed 3 cps spike and wave discharges.

N. was described by his parents as a boy who, except for his seizures, was customarily conforming to their standards, though clinging and demanding of indulgence. He was adjudged by psychiatrists who had seen him previously on consultation as "very immature and rather effeminate" and as "a boy with whom it was difficult to establish close rapport." He was an only child.

Psychiatric studies of the mother revealed that she was a compulsive, perfectionistic person, whose relationships with others were characterized by very little investment on her part except for what support and approval others might give her. She was inclined to be overindulgent and unduly intimate in N.'s rearing. She kept in constant attendance during his baths and frequently undressed in front of him or slept with him up to the time he began psychologic treatment. On the other hand, she showed poor tolerance to the least signs of hostility he manifested toward her. She encouraged him to learn to cook and do housework. She had a tendency to tell him in what respects she considered the father inadequate.

The father was a passive, self-depreciative person who had difficulties in dealing with men in competitive situations or adequately asserting himself when someone's demands were actually excessive, e. g., an employer's. As the oldest son in the family, the father had had to take over the financial support of his siblings at the age of 15 because of the economic failures of the paternal grandfather, a temperamental, chronic alcoholic. In psychotherapeutic sessions with a male social worker, it developed that the father had the idea the patient wanted to replace him, just as the father had replaced the paternal grandfather. The father defended himself against rivalry with his son by constantly giving him gifts, exposing him—if not pushing him—to the mother's confusing intimacy, aloofness, and compulsive demands for cleanliness and orderliness. Though the father wanted to do so, he had difficulty in experiencing a warm interest in and real companionship with his son.

Events Occurring at the Onset of Patient's Seizures.—The onset of N.'s first seizures ("screen spells") occurred at the age of 5 years, in 1943, shortly after the father departed for active duty in the Army. Interviews with the mother revealed that at this time she turned to

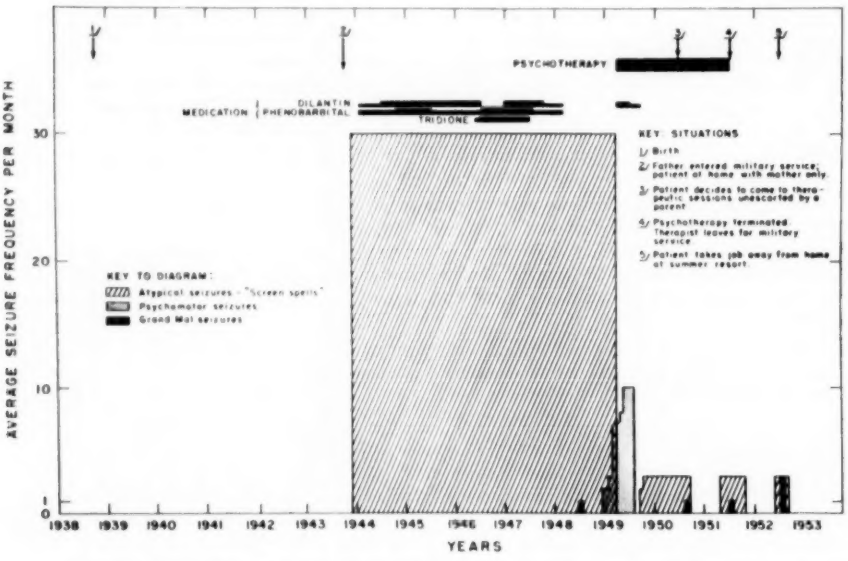

Chart 2 (Case 2).—Diagram summarizing the temporal relations of therapeutic events to average seizure frequency.

the patient for security and that she also directed some of her anger aroused by her husband's leaving at the patient. Her inconsistent seductiveness and compulsive restraint were most pronounced toward him at this time.

No life situations of significance are known to have occurred during the time of onset of N.'s grand mal seizures, at the age of 9 years, and his psychomotor seizures, at the age of 10 years.

Effect of Anticonvulsant Medication on Clinical Manifestations Before Start of Psychotherapy.—From the time of onset of his first seizures, i. e., the "screen spells," many of the standard anticonvulsant regimens, including use of a ketogenic diet and administration of bromides, phenobarbital, diphenylhydantoin, or trimethadione (Tridione), or combinations of these, had been tried. Such medication had effected no essential change in the frequency or form of his seizures (Chart 2). However, at the time psychotherapy was started, in March, 1949, he had not taken any medication regularly for about one year, being given only a capsule of phenobarbital (30 mg.), usually after a fit.

Because of the distressing effect on his parents of the destructive aspects of his psychomotor seizures at the time psychotherapy was started, another trial of diphenylhydantoin medication was made—diphenylhydantoin, in a dose of 0.09 gm. twice a day. With the disappearance of the psychomotor spells after the first five or six months of psychologic treatment, the administration of diphenylhydantoin was discontinued. No anticonvulsant drug of any sort was administered during the remainder of the course of psychotherapy.

Changes in Clinical Manifestations During and After Psychotherapy.—At the initial interview, N. was observed to be large for his age, plump, pink-skinned, with regular facial features. He wore glasses. Throughout the session he kept a knit cap on his head. He was restless and moved about the playroom continually, sometimes apparently for purposes of exploration and orientation, but oftener without discernible reason. He glanced out of the playroom window through the window screen furtively, without any immediate or discernible reaction. He then began playing actively with a dart gun and holster, while explaining he had seen several doctors previously at the Clinic. It seemed, he explained, that he had "hypnotic powers," could hypnotize himself by looking through a screen, "a habit, very silly." He went on to say that he wanted to get rid of the habit because Dr. H., his pediatrician, told his mother he should. As soon as any questions were asked, he regularly responded with the remark, "I don't know," but often later would spontaneously elaborate with a more detailed and pertinent answer. He volunteered tensely that he liked to come and see doctors, psychiatrists, because he liked "to be amused." When his next responses were awaited without his implicit plea to be entertained being satisfied, he remarked petulantly, "I love to play and amuse myself." He did so for a while with different play materials. Returning to the gun and holster and strapping it onto himself, he tried pulling out the gun rapidly and pulling the trigger, observing that he had to practice because he "might be slow on the draw, the gun could get caught in the holster. . . happens sometimes to cowboys." At the close of the session he said he had to shoot the dart gun four or five more times. He did so and then observed, in a tone of threatening reminder, "I like to be amused so much; do I have to go?"

Summary: 1. During the first three months of treatment the "screen spells," which had occurred one to several times a day, became decreasingly frequent and disappeared for about six months. In the meantime the psychomotor seizures became more frequent, the number ranging from two to eight a month. No grand mal seizures occurred during this period. Then, as the patient began to be able to communicate the various components of his psychomotor seizures, i. e., the thing he was doing and what feeling he had about it at the moment just preceding his psychomotor spell, and what he did, thought, and felt during and after the seizure, his psychomotor seizures disappeared fairly rapidly. No further frank psychomotor episodes occurred after the fifth month of psychotherapy. In view of this, the diphenylhydantoin sodium, which had been administered with the beginning of psychotherapy, was then discontinued. In these circumstances, no recurrence of the psychomotor fits was noted. Situations which previously had been followed by psychomotor spells were then followed by typical temper tantrums, which the patient could describe and discuss fully. He could also give a more detailed report of his emotional reactions during the temper tantrums. The incidence of these temper tantrums gradually decreased during therapy and became progressively milder and briefer. During the last 18 months of treatment they occurred only rarely.

2. On the other hand, as psychomotor seizures waned and disappeared, the "screen spells," which had practically stopped at home, began to recur about the fifth to the sixth month of treatment, tending for a while to be confined to the therapeutic sessions in the playroom. Much less frequent than previously, but definitely paroxysmal in nature, these spells began to change in character during the therapeutic sessions. The patient could terminate one of these seizure states if the therapist requested him to do so. He began to be able to communicate freely his thoughts, fantasies, and feelings during the seizure. Although sometimes he would deny knowing what neuromuscular activities he had just performed, when the therapist described to him what he had done, he began to integrate this information into his discussion and evaluation of the matter. Oftener, he spontaneously volunteered observations about one or another aspect of his motor activity during the spells. In these circumstances, he demonstrated the ability to control the time when a "screen spell" would start; i. e., he could prevent or let the paroxysmal motor activity occur while looking through the screen, he could generally stop such activity at will, and frequently he interrupted it to talk with the therapist and then resumed the motor activity characteristic of this convulsive state.

Furthermore, the form and pattern of these seizures changed. Instead of the stereotyped extensor movements of his arms and the flexor movements of his head and neck, this paroxysmal motor activity became more complex and highly organized, and he was able to verbalize simultaneously with this activity appropriate ideation and feeling. When, for instance, the "screen spell" consisted mainly of coital movements with flexor movements of his head and neck, he observed that he was moving "like a hula dancer," and much of his interseizure and other intraseizure verbalizations were related to inhibited heterosexual aims. During the period when he was talking about masturbatory problems, there occurred seizures during which he manipulated his genitals through his trouser pockets or clutched and grabbed at his buttocks with one hand and with the other hand fingered his genitals. Another time, when he was obviously enraged and anxious, he had a "screen spell" during which he stood before the window screen, his arms akimbo, hitting his thighs and knees forward on the wall, ducking, and often banging his forehead on the edge of the raised window. Suddenly he interrupted this activity and reported anxiously that he felt as though the wall had moved outward, that he had knocked it out by the strength of his movements.[6]

3. Various modifications in the characteristic behavior of the patient occurred. He began to communicate his ideas and feelings more intelligibly. He confided being terrified at times by his own "crazy thoughts," predominantly destructive urges. Instead of exhibiting a habitually submissive behavior and seeking to be entertained, he became increasingly assertive and spontaneously made bids for more independence and self-determination. He got a part-time job after school as a delivery boy. He tested his parents in various ways. He went through a brief period of mimicking and caricaturing his father and his mother in their usual ways of interacting with him. He began asking many questions of the therapist, generally with evidence of much anxiety. He eventually asked the therapist for sexual information and revealed his own anal theories of conception and birth. Frequently, in the playroom, when the therapist could help him formulate a question or the reason for very strong unacceptable impulses, a "screen spell" was averted or aborted.

At the time of discontinuation of psychotherapy, he had achieved a more congenial companionship with his father, and his adjustment at school with his freinds was better. The situation with his mother was improved, but he was experiencing distressful, ambivalent feelings about her. "Screen spells" now occurred infrequently at home, and they occurred rarely in the playroom. As previously mentioned, no psychomotor spells had recurred for two years.

It is perhaps interesting that each of the two grand mal seizures that occurred during this period of 28 months of psychotherapy appeared at a time when N. made decisive efforts toward independence and self-reliance. The first grand mal spell occurred after 18 months of treatment, specifically after an interruption of therapy during summer vacation. Continuation of treatment had been made contingent on his own decision to come (at his insistence), and without either parent accompanying him, as one had previously done regularly. The therapist telephoned him, and N. stated that he had decided to continue treatment and come to the therapeutic sessions without either parent. The next day—the day before his appointment— he had a major seizure at home. The day after final termination of psychotherapy, also, although he was superficially gleeful about the ending of treatment, because he regarded the termination as a sign of maturation and development, he had another grand mal seizure. N. understood that the therapist was leaving for military service, as N.'s father once had done, but he did not consider this of any

6. With repeated observations on, and communications with, N. during, before, and after his "screen spells," I became aware of the inadequacies of the current terminologies referable to explosive neuromuscular, ideational, emotional, and vegetative discharges in subjects with demonstrable interseizure electroencephalographic abnormalities. To what extent "hysterical" seizures and "temper tantrums," and even less striking behavioral activities, shade into, may be superimposed on, or may be indistinguishable from "true, or genuine, epileptic" phenomena is difficult to evaluate. (Attention has already been called to the similarity of these various kinds of sudden, transient activities [Bartemeier [3b]]). The present report does not propose to deal extensively with the semantic confusion and difficulties in differential diagnosis in this borderland region of investigation of neurology and psychiatry or neurophysiology and psychology, but the matter is brought up at this time to indicate a problem in nomenclature, designation, and connotation which will need further clarification.

consequence. One year after the termination of psychotherapy, in July, 1952, at the age of 13 years 10 months, with his parents' permission, he went away from home to a summer resort to work as a bus boy and waiter. There he soon had a series of three or four grand mal seizures, each one occurring after he felt compelled to stare through window screens. Initially, he had a typical "screen spell," during the course of which a frank grand mal fit occurred.

The psychotherapeutic investigation of this patient provided some information as to the origin of the looking behavior as a trigger for the "screen spells." Seeking to look at his parents having sexual relations had been a temptation presented to him between the ages of 3 and 10, when he had occupied a bedroom adjacent to his parents' room, his bed being so situated that he could see his parents' bed in the next room. The adjoining doorway lacked a door when he was 3 to 6 years of age, but a clear view was irregularly obscured by a decorative, checkered screen! He had no conscious memory of witnessing parental intercourse, but he had a strong forbidding urge to do so. In his looking through window screens he had confusing fantasies of being beaten by God or some powerful person and fantasies of assuming either the male or the female role in the sexual act. His concept of the sexual act was that it was a sadomasochistic performance. He anxiously confessed that he had a powerful urge to see women tortured. He wondered why gangsters did not have sexual relations with women they killed. He attributed magical and omnipotent powers to the acts of looking and being looked at, reacted as though he could control or hurt others by looking, and feared equally potent retaliation through being looked at by others. The following further observations relevant to the psychologic activating factors of N.'s spells can be made.

Screen Spells: A characteristic chain of events was observed to culminate in screen spell in the playroom. 1. N. would be either engaging the therapist in some play or talking with the therapist. In this interaction an incident would occur which N. would presumably experience as a "deprivation," [7] the depriving agent being either someone that N. was telling the therapist about or the therapist himself, e. g., the therapist or someone else did not fulfill some explicit or implicit demand of N.'s. 2. The pattern of N.'s immediate activities would abruptly change, whatever he was doing and/or saying. He would turn and walk toward the window, on reaching it would glance slightly upward through the screen, and would often reiterate that at times he was unaccountably and irresistibly drawn to the screen. 3. Generally, staring less than one-half minute through the screen did not lead to a typical screen spell. During this half-minute, verbal interchange with N. was open. When questioned, he never saw any relation between his feeling of compulsion to go to the screen and the context of the immediately preceding interactions with the therapist. He never volunteered that he experienced any feeling of anger, fear, or frustration. In fact, he usually denied any such feeling when he was asked. But an accurate and acceptable interpretation of the preceding situation and N.'s presumably covert aims and feelings could at this point prevent the development of a screen spell. 4. If N. looked through the screen for longer than about one-half minute, a screen spell of varying duration invariably occurred.

Grand Mal Seizures: Grand mal seizures were never observed in the playroom. In all instances in which they occurred, however, it was observed by his parents, or other observers, that grand mal fits developed sometime during prolonged screen spells. Psychiatric investigation added the information that the infrequent grand mal seizures tended to occur during a period when N. had been making efforts, often premature, toward independence from parental control and support.

Psychomotor Seizures: No psychomotor seizures were observed during sessions in the playroom. Retrospective verbal comments by N. about the situations and his personal feelings and aims just preceding the onset of such seizures gave evidence that a sequence of events obtained somewhat similar to those with the screen spells. That is, N. experienced some "deprivation," which was shortly followed by a psychomotor seizure. The deprivation, as reported by N., was typically of trivial variety. For example, on one occasion he reported that he had been listening to a cowboy radio thriller and the program was interrupted by the announcer making a commercial; N. felt furious, briefly, at the interruption, and a psychomotor seizure ensued. N. could not report what he did during the seizure. Only his parents could give a description of the

7. The term "deprivation" is used in a broad sense to include any state or situation in which one could reasonably infer that N. experienced a lack of indulgence, failure to reach a goal, or frustrating experience.

behavioral details. Nor could N. recall any of his thoughts or feelings during the seizure episode. On another occasion, he reported he had been bouncing a tennis ball against a backboard. He missed several shots, felt furious, and started to break his tennis racket. A psychomotor seizure, with the usual wantonly destructive components, followed.

A perhaps essential differentiating characteristic of the intervening variables in the psychologic trigger associated with the psychomotor seizure as distinguished from the screen spell was the fact that N. could report feeling angry (out of proportion, of course, to the situation) just before the onset of the psychomotor spell, whereas he was aware of no emotion or frustration just before the onset of a screen spell—only a compulsion to go to and look out of a window screen.

Electroencephalographic Report.—1. Before Psychotherapy (January, 1945; age, 6 years 4 months): "The record shows 10-cps activity, with short runs of 4- to 6-cps activity, and an occasional petit mal seizure discharge, slightly more pronounced in the right hemisphere, but no reliable focus of abnormal activity. During spontaneous sleep, petit mal discharges appear more numerous. There is large build-up with hyperventilation. The impression is that of an electroencephalogram which is fairly normal in frequency, with petit mal seizure discharges." (F. A. Gibbs)

2. Before Psychotherapy (July, 1945; age, 6 years 10 months): "The record is similar to one taken in January, 1945, with occasional petit mal seizures discharges. Placing of the screen in front of the patient produces no changes clinically or in the electroencephalogram and no more seizures discharges than before. The impression is that of petit mal discharges." (F. A. Gibbs)

3. Before Psychotherapy (December, 1948; age, 10 years 3 months): "The record shows 9- to 10-cps waves in the occipital region and bursts of 3- to 4-cps waves in all leads, most pronounced in the occiput. No focus of abnormality is found. There is a moderate build-up with hyperventilation. The impression is that of an abnormal curve consistent with a diagnosis of epileptic disorder of unspecified type." (H. M. Serota)

4. During Psychotherapy (September, 1949; age, 11 years): "The record shows bilateral 9- to 10-cps occipital rhythm, reflected in the anterior leads. High-amplitude, 6-cps waves appear in frequent sequences, diffusely. Slower waves, of 3- to 4-cps frequency and often spike-like in form, arise principally from the occipitoparietal region bilaterally. There is moderate build-up with hyperventilation. The impression is that of paroxysmal discharges, highly consistent with a convulsant disorder." (H. M. Serota)

5. After Psychotherapy (Oct. 16, 1951; age, 13 years 1 month): "A sleep record was not obtained. There is 9- to 10-cps activity, with considerable irregular slow activity and occasional sharp wave-and-spike activity of low to medium voltage. In longitudinal leads, spikes and sharp waves are primarily seen in the right parietal area. Slow activity tends to appear in the right parietal area and in the temporal area bilaterally. There are occasional diffuse complex paroxysmal bursts. With hyperventilation there are improvement of alpha rhythm and reduction of slow activity. The impression is that of focal slow activity in the right parietotemporal region, with paroxysmal spikes and sharp waves of low voltage in the right parietal area. The character of the minor paroxysmal abnormalities suggests a deep or subcortical, rather than a superficial, lesion, probably right-sided, as does the continuous slow activity. It is suggested that the lesion is either deep to the right temporoparietal cortex or in a subcortical system having the same projection." (J. P. Toman)

Psychological Tests.—Stanford-Binet Scale, Form L: The results were tabulated.

	June 27, 1945 (Before Psychotherapy)	Sept. 19, 1951 (After Psychotherapy)
Chronological age	6-9	13-0
Mental age	7-0	14-0
Intelligence quotient	104	108

Rorschach Tests (Dr. Samuel J. Beck).—Two Rorschach tests are evaluated.

Rorschach Test 1 was done when the boy was 10 years 3 months of age (before psychotherapy). The findings reveal that the patient rigidly inhibits the expression of feelings. There is a relative absence of association to human forms. He shows an inability to verbalize personal

matters. In summary, there is a striking inadequacy of personality development, marked furthermore, by perceptual departures, attention lapses, and rigid thinking processes. When emotional stresses occur, such symptomatic behavior is to be expected.

Rorschach Test 2 was done when the patient was 12 years 11 months of age (after psychotherapy[8]). The findings show that psychologic conflict and free anxiety are definitely more prominent, although rigid defenses and a tendency to withdraw from human relationships persists. But in the second test the expression of feelings and impulses is out in the open. In contrast to the results in the first test, there is considerably more willingness to master primitive urges, in spite of consequent painful tensions and anxiety. Psychotherapy should be continued.

CASE 3.—R., an adolescent boy, born July 24, 1930, was 17 years 10 months of age when psychotherapy was started, on May 18, 1948. He was seen regularly once a week for two years and thereafter about once every two weeks for a total of a little more than 100 therapeutic sessions.[8] His psychotherapeutic treatment was interrupted May 2, 1951, because the therapist had to leave the city permanently.

Diagnostic categories which roughly describe or classify his personality disorder include (1) idiopathic epilepsy, grand mal type, and (2) schizoid character disorder.

Clinical Manifestations Before Psychotherapy.—Ictal manifestations before the period of psychotherapy consisted of grand mal seizures, which began at the age of 17 months and occurred once or twice a month.

Other notable behavior and personality manifestations were presented: 1. Calling telephone operators impulsively and making obscene and hostile remarks to them. This behavior began in August, 1947, occurred about 30 times, and lasted four months, until R. was apprehended by the police and referred to the juvenile court. Incidentally, he was referred to the psychiatric clinic for treatment because of these episodes. 2. Occasional uncontrollable and inappropriate giggling for brief periods. These spells were observed at home and during therapeutic sessions for the first six months. 3. Insistence on his being subsidized so as to get training as a musician. R. was evaluated by his music teachers at school as having limited aptitude and very little skill as a musician at that time. (His instrument of choice then was the trumpet.) Furthermore, he was in the process of failing his senior year in high school.

Possible Pathogenic Factors in the Epileptic Syndrome.—There was no familial history of epilepsy or migraine or history of birth trauma. At the age of 6 months he had had a severe attack of pneumonia, requiring a month's hospitalization. At the age of 17 months he had his first grand mal seizure, and these attacks continued to occur on the average of about 12 a year until the ages of 8 to 13, when their frequency ranged from 25 to 40 a year. A decrease in the annual seizure frequency to 20 to 30 a year followed the administration of regular anticonvulsant medication, started at the age of 13.

At the age of 4 years a developmental visual defect was first noted, i. e., ambylopia and esophoria of the left eye; this has persisted unimproved. In addition to these findings, ophthalmologic examinations revealed "an old chorioretinitis" in the left eye.

At the age of 6 years he fell off his bicycle and hurt his left hip. Medical examination revealed aseptic necrosis of the head of the left femur (Legg-Perthes disease; osteochondrosis of the capital epiphysis of the femur). He became completely dependent on his mother for day-to-day care. When he was 7 years old, his mother became pregnant, and she felt she was unable to care for him efficiently during the latter part of her pregnancy. It was at this time that he was hospitalized for treatment of his hip disease for seven months; this resulted in a structural recovery of the joint lesion and the full use of his extremity. In the hospital, he had feeding difficulties, often refusing to eat. At the age of 8 years, on returning from the hospital, he first learned that he had a baby sister, 2 months of age. Although at first he expressed interest in his new sibling, he shortly became upset, when he found he was receiving considerably less of his mother's usual attention. The frequency of his seizures was immediately greater and continued so during the ensuing years. An electroencephalogram obtained at the age of 16½ years was considered consistent with the diagnosis of an epileptic disorder.

8. It was the impression of the therapist that when any more frequent treatment interviews were attempted with R., there was mobilized either such anxiety or regression to such a dependent orientation that either treatment progress was acutely interfered with or the frequency of convulsions was acutely increased.

The parents' attitude towards R. was that he was incurably tainted. The mother was too ashamed ever to tell relatives that R. had epilepsy. She kept him from meeting them. She did not allow him to participate in any physical recreation whatever during his years of schooling. She would not let him seek any kind of gainful employment for fear he would have a seizure. Collaborative psychiatric treatment of the mother by a psychiatric social worker revealed that she showed intense and pervasive hostility, feelings of inferiority, unusually strong desires to improve or maintain social status, and fears of impoverishment. (The father actually did have to struggle to make a living as a newspaper vender.) She constantly refused to permit the patient independence and emphasized his physical limitations. Yet she criticized his failure to achieve independence. Furthermore, she incited trouble between the patient and his sister, provoking them to fight with one another for her attention.

Events Occurring at Onset of Patient's Seizures.—The available data indicate only that R.'s seizures began at the age of 17 months 9 months, after a severe bout of pneumonia, requiring hospitalization. An increase in the frequency of seizures at the age of 8 years, from an average

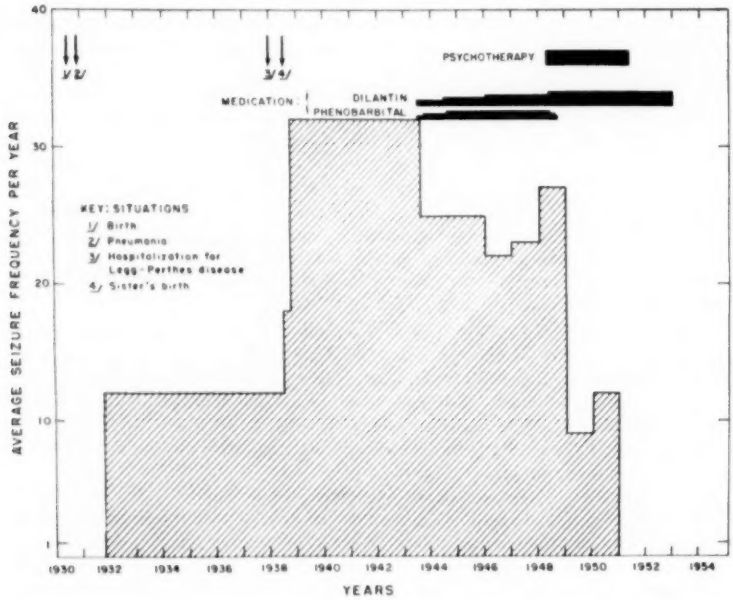

Chart 3 (Case 3).—Diagram summarizing the temporal relations of therapeutic events to average seizure frequency.

of 12 to one of 25 or 40 a year, was temporally related to a long period of hospitalization for Legg-Perthes disease and the birth of a sibling.

Effect of Anticonvulsant Medication on Clinical Manifestations Before and at Beginning of Psychotherapy.—At the age of 13 years, R. began receiving anticonvulsant medication in the form of diphenylhydantoin sodium and phenobarbital, in variable dosage, with some reduction in the seizure frequency, i. e., from 35 or 40 to 20 or 30 seizures a year. For about one year before psychotherapy was started, he was receiving diphenylhydantoin sodium, 1½ grains (0.9 gm.) four times a day, and phenobarbital, 1½ grains three times a day.

In 1946 he had a total of 22 major seizures; in 1947, a total of 23 grand mal attacks.

Within one month after psychotherapy was started in May, 1948, the anticonvulsant medication was changed to use of diphenylhydantoin sodium, 1½ grains five times a day, and no phenobarbital was administered. The total number of seizures during 1948 was 27. These

seizures, in contrast to those in preceding years, began, during the latter part of 1948, to occur as a series of several a day, with increasing length of of the seizure-free intervals, instead of as isolated seizures at more frequent intervals.

Changes in Clinical Manifestation, During and After Psychotherapy (Fig. 3).—At the initial interview R. presented an unkempt and strangely ape-like appearance. At first he was very slow-moving and sat stiffly in his chair, with a fixed facial expression. Gradually he tended to flex his extremities and body to assume a position with his head resting on his arms, which were folded on the table. From this position he would glance up at the examiner from time to time without moving the rest of his body. At first his verbal spontaneity was very low, and intervals of two to three minutes would follow his laconic replies to questions. He gradually showed more spontaneity and talked at greater length, but relative retardation in the frequency and latency of his verbalizations continued. There were few variations in facial expression or bodily posture until emotion-provoking subjects came under discussion. Then he would straighten up, cross his legs, and look away. His cheeks would redden slightly. He would drum with his fingers on the table or on his arms and hum in a distracted fashion, and yet respond relevantly to the conversation. He talked about his seizures. He described his aura, stating that he experienced a sudden feeling of hunger, slight nausea, and "shivering," with cold sensations up and down his spine and the back of his legs. The attitude expressed toward his seizures was one of rebellious resignation. He did not know why he had made the telephone calls to telephone operators. He felt ashamed and guilty at having said abusive things to "people who did not deserve them." He passed off further discussion of this matter with the remark that these episodes were "like my grand mal seizures—I don't know what causes them." He then mentioned his annoyance and chronic rivalry with his only sibling, a sister eight years younger than he. He stated that his parents, especially his mother, formed an alliance with his sister against him.

During the first year of psychotherapy, R.'s activities in the treatment sessions consisted primarily of testing out how reliable a person the therapist was. By devious, rather than direct, means he began extracting proof from the therapist that he was acceptable and likable. He spent many sessions gazing dreamily at the therapist and occasionally asking questions about situations at school and at home. His declarative statements were generally limited to difficulties in getting along with his sister and the unreliability of his mother. Because he was so disorganized and insecure, he was permitted to proceed in this way. His questions became more frequent, stereotyped, and irrelevant, and he became more animated and demanding. He would ask for the chemical formula of medical drugs or the definition of words.

A dramatic elimination of R.'s seizures occurred for a period of six months, as long as the therapist was permissive and continued giving verbal responses when R. signaled with a question that he wanted the therapist to say something, anything. Eventually, with a refusal on the part of the therapist to answer the more irrelevant questions and his insistence on determining their underlying motivation, the patient had frequent seizures, several occurring a day. The seizures closely followed commonplace, extratreatment incidents which had special, often symbolic, significance for R.; e. g., his mother changed the dairy from which she bought chocolate milk for the family, his sister forgot to buy the ice cream she was supposed to get for supper, or he read in a musicians' periodical that certain union members were in default of their dues and therefore subject to suspension from the musician's union.

Then R. began to be aware of his inordinate need for support and acceptance. He told episodes of his childhood that revealed a strong sense of parental, particularly maternal, rejection. He reported feelings of confusion about his worthiness. On the other hand, he related isolated instances from his earlier childhood (before his sister's birth), when he felt soothingly protected and indulged by his mother. In association with these memories, he reported recurring daydreams of himself as a great and highly celebrated person.

From the beginning of psychiatric treatment, R. had expressed wonder that people made such a stir about the difference in the sexes. He now declared there was no essential difference between male and female. Certainly, he insisted, they both had a penis. He thought he had seen his sister's penis. Such open naiveté about anatomical differences in the sexes in a 17-year-old boy might have been considered suspect. But the evidence was convincing that, so far as the patient's reportable knowledge of such matters was concerned, he knew of only one sex, ana-

tomically speaking, and could not believe that there should be any other structural possibility. His first dream during treatment indicated that he was curious to know but that his acquisition of information was blocked.

"I was going up some dark stairs. At the top there was a dark corridor. On either side was a door. I knew one was a men's toilet. The other was for women. The door to the women's room was a little open, and I started toward it and woke up with a start. But this is a dream. I've had it many times. I always wake up at that point."

The origin of this specific inhibition of acquiring information could then be supplied by the patient in certain memories of childhood. Until he was 5 years of age his mother had regularly taken baths with him because, as he understood it, she wanted to be near enough to him to protect him if he had a seizure at such a time. When he began to ask questions about anatomical differences and childbirth, she abruptly stopped taking baths with him and watched over him from the outside of the tub. She warned him never again to come into her room when she was dressing or when she was bathing. She emphatically denied that there was any difference in the roles of the sexes in childbearing and did not supply information pertaining to any mutual contribution of the sexes in procreation. R.'s view of childbirth was, for instance, that some people can have babies and some cannot, regardless of sex. The sharp interruption in his day-to-day experience of receiving his mother's care, occasioned by his long hospitalization and the arrival of a baby sister when he was 7 or 8 years old, reinforced an early, chronic childhood premonition he had had (the basis of which was not learned and cannot now be established without speculation) of some sense of catastrophic deprivation. Therefore, various life experiences, such as the withholding of information he requested, the denial of a tension-relieving verbal reply when he made a verbal request, his mother's changing of his brand of chocolate milk, the refusal of someone to do all his homework for him, and the refusal of the therapist to let him study his clinic chart, were presumably experienced by him as serious deprivations and evidence of the unreliability of a parent or a parent surrrogate. Situations of this sort, or with some common denominator, were repeatedly found to trigger his gastric aura and his grand mal seizures. Biochemical or other factors apparently determined whether one or several such life experiences were adequate to precipitate a seizure. After the therapist had achieved some degree of success in illustrating and promoting partial understanding of his inordinate demands for acceptance and support and his feelings of deprivation, a notable decrease in the seizure frequency occurred.

That the period of psychotherapy played a key role in bringing about symptomatic improvement is evidenced by the fact that with psychotherapy this boy, whose seizures had never previously been controlled adequately by anticonvulsant medication, had about one-half the usual number of fits in 1949 and 1950 and had no seizures whatever in 1951 or 1952 on approximately his usual dose of anticonvulsant medication. Incipient strivings to emancipate himself from his deep insecurities and from the home where his conflicting drives and maladaptations were nurtured are perhaps indicated by his last dreams in treatment, when he was dealing with the problem of achieving some financial and emotional independence of his parents:

"I had something like a chicken, although much smaller than a chicken. More like a homing pigeon. I let it go out of the house to fly around where it wanted to, and to test out whether it could find its way back.

"I had some gas balloons, tied a note to them with my name and address, and let them go out of the window. I was just curious to find out whether the notes would be returned to me, so I could find out how far the balloons had gone."

His associations centered around his wish to become independent of his family and of his anxieties about certain realistic aspects of an epileptic person's getting and keeping regular employment.

During the period of treatment, the patient graduated from high school and attended one year of junior college. He continued his study of music—on his own—and actually did satisfy the qualifications and become a member of the Chicago musicians' union. Later, because of difficulties in securing employment as a musician, he studied to be a masseur, by this time getting some, perhaps misguided, encouragement and financial support from his parents. Blocked in obtaining employment as a masseur, he finally accepted employment as a clerk and was holding his first position of gainful employment when psychotherapy was stopped.

At this time, still a strange-looking person, and still in conflict psychologically, he was no longer so unkempt, retarded, or frankly withdrawn and dissociated. He could communicate his wants, feelings, and fantasies and could appraise his life circumstances more realistically.

The psychologic factors associated with R.'s seizures may be summarized. R. was fixated at a dependent stage of development. His demands for food, affection, and support had hostile components. The mobilization of receptive and dependent impulses occasioned both guilt and fear of loss of love. Examples of R.'s often disorganized and devious attempts to solve his conflicts are described. Parental attitudes of rejection and fear about R. and the meaning of his seizures contributed to his insecurity. Everyday events that R. experienced as evidence of the unreliability of a parent or parent surrogate were found to trigger his gastric aura (a sudden feeling of hunger and slight nausea), which, in turn, was often followed by a grand mal seizure.

Electroencephalographic Report.—1. Before Physiotherapy: (*a*) December, 1946 (age, 16 years 5 months). "The record shows bilateral 10½-cps occipital rhythm, with a suggestion of 3- to 4-cps occipital rhythm. There is no build-up with hyperventilation. The impression is that of a possible abnormal curve, with numerous artifacts. The patient cooperated with difficulty." (H. M. Serota)

(*b*) January, 1947 (age, 16 years 6 months). "The record shows an 11- to 12-cps occipital rhythm, with occasional bursts of 4- to 5-cps bilateral frontal activity. There is a large build-up with hyperventilation. The impression is that of an abnormal curve consistent with the diagnosis of a convulsive disorder." (H. M. Serota)

(*c*) April, 1947 (age, 16 years 9 months). "The record shows a 10-cps occipital rhythm, with definite 3- to 5-cps frontoparietal rhythm in paroxysmal bursts and slow random potentials. There is a slight build-up on hyperventilation. The impression is that of a definitely abnormal curve consistent with the diagnosis of a convulsive disorder." (H. M. Serota)

2. During Psychotherapy (July, 1949; age, 19 years): "The record shows a 12-cps occipital rhythm, with diffuse occasional 4- to 5-cps activity. There is a moderate build-up with hyperventilation. The impression is that of an abnormal curve consistent with diagnosis of an epileptic disorder. However, the record shows definite improvement over the curves for January and April, 1947, with a tendency toward diminution of slow and paroxysmal activity." (H. M. Serota)

3. After Psychotherapy (May, 1951; age, 20 years 10 months): "The waking record shows 9- to 10-cps occasional slow and sharp activity in the frontal and temporal leads, especially in the left anterior temporal area. The sleeping record shows low-voltage fast and irregular slow activity. With hyperventilation there is paroxysmal sharp and slow activity. The impression is that, except for the hyperventilation sensitivity, this record shows some improvement over previous electroencephalograms." (J. P. Toman)

Psychological Tests.— Wechsler-Bellevue Intelligence Scale: The results are tabulated.

	Nov. 25, 1946 (Before Psychotherapy)	Aug. 13, 1951 (After Psychotherapy)
Intelligence quotient	93	96
Verbal	117	120
Performance	67	70
Chronological age	16-4	21

The remarkable aspect of the results of these two tests is their extreme similarity. The only significant difference is the marked improvement in arithmetic. The shifts in the performance series, for better or for worse, are not very great, although an improvement in picture arrangement (social comprehension and grasp of cause-and-effect relationships) may be important for this boy.

Rorschach Tests (Dr. Samuel J. Beck).—Two Rorschach tests are evaluated.

"The first Rorschach test was done when the boy was 17 years 4 months of age (before psychotherapy). The data of the test reveal a withdrawal of emotional contact and expression from the outer world, erratic perception and attention, and regressive thinking. In addition, there are a rigid character structure and inhibition of pleasurable responses.

"Anxiety is mobilized most acutely to the 'mother' figure but is also apparent toward the 'father' figure, toward which an ambivalent attitude is suggested.

"His vulnerability to the color stimuli suggests a reactive or neurotic personality structure.

"The second Rorschach test was done when the patient was 21 years 1 month of age (after psychotherapy). It indicates that strong urges and feelings have been freed from repression and that the patient can now enjoy relations with other persons. On the other hand, there persists many signs of disturbances in personality functioning, e. g., serious inaccuracies, deviations in thinking, unique or irrelevant elaborations, and flight of attention. His response to the test has progressed from an immature to a 'neurotic' reaction pattern, in which there is now evidence that when he experiences strong emotions he has conflicts about expressing them.

"Although there is considerable improvement in this patient's personality, the whole picture is not that of a well-integrated person."

COMMENT

Modifications in Seizure Frequency Induced by Psychotherapy.—A review of the changes in seizure frequency and the requirements of anticonvulsant medication during and after the period of psychotherapy provides evidence that the seizure threshold of each patient was increased. It cannot be proved in this study that the passage of time alone or in combination with an anticonvulsant medication was not of some consequence in effecting this change. The evidence that the psychotherapeutic activities contributed to the clinical changes is provided by the fact that variations in the psychotherapeutic management of each child were associated with reversible changes in the frequency of his convulsive manifestations. Moreover, there were notable differences in the dosage of anticonvulsant medication the children received before psychotherapy and the types of convulsive behavior they manifested. Nevertheless, they all showed a decrease in seizure frequency with psychotherapy.

It is unfortunate that critical intergroup control experiments could not be run in such a study as this, so as to demonstrate decisively and exactly the effect on seizure rate of passage of time alone, and of psychotherapy alone, on large groups of perfectly matched pairs of patients. But the infeasibility of such an attempt is obvious. As a result, in this investigation some compromise in scientific rigorousness, such as the use of a patient as his own control, seemed necessary.

Some comment on the interseizure electroencephalographic studies is necessary. Such records supply neurophysiological evidence of the paroxysmal or epileptic nature of each child's convulsions. They do not help to clarify with certainty which behavioral manifestations were accompanied by disordered cerebral electrical potentials and which were not. But they do substantiate the idea that each of these three patients had a deviant or pathological pattern of electroencephalographic activity.

When N. (Case 2) was at an age when he was having only "screen spells," the electroencephalographic reports indicate that the form of cerebral electrical discharges recorded from his scalp were typical of "petit mal" discharges. But most readers would hardly recognize the patient's "screen spells" as typical petit mal seizures. These "screen spells" had features indistinguishable from such syndromes as hysterical convulsions or fugue states. To these conditions is imputed primarily, if not solely, a psychogenic basis. It is my opinion, based on both the interseizure electroencephalograms and repeated observations of the "screen spells," that the occurrence of these "screen spells" was determined both by biological factors—structural and/or functional—and by experiential, or psychologic factors. Not one, but an interplay of all these factors, was necessary for the ictal phenomena to occur.

The improvement in the electroencephalograms of K. (Case 1) with psychotherapy is interesting. This child happened to be the one receiving the most intensive psychotherapy in terms of sessions (three to four a week). He showed the most dramatic change in personality of the three patients treated. Furthermore, he was the youngest child. It would be tempting to conclude that the beneficial effect of psychotherapy was reflected, at a neurophysiological level, in his electroencephalogram. To draw such a conclusion would be unjustifiable, however, for a "fairly large percentage of patients" with a spike discharge focus in the midtemporal area have, within five years, a presumably spontaneous disappearance of this focus.[9] The significance of the improvement in the electroencephalograms in Case 3 must also await evaluation. Further studies must be made to establish whether or not psychologic procedures can modify paroxysmal electroencephalographic patterns.

Modifications in the Form of the Seizures During Psychotherapy.—The idea that the form of epileptic seizures in a patient may change in relation to other events is not new. The administration of one type of anticonvulsant drug has been observed to inhibit the occurrence of one kind of seizure and increase the frequency of a different form of paroxysmal manifestation.[10] Psychotherapy has been reported to modify the form of the convulsive episodes in a patient with petit mal seizures. In this report the chronological sequence of changes in the form of paroxysmal manifestations during psychotherapy were petit mal seizures, grand mal seizures, psychomotor "acting out," narcolepsy, and various conversion manifestations or anxiety attacks.[3a]

The present study gives additional evidence that children subject to convulsive tendencies may show, in relation to intervening events, such as psychotherapy, alternative forms of repetitive, explosive behavior and sensory activity. In Case 1, the disappearance of nocturnal grand mal seizures and petit-mal-like spells was followed by temper tantrums, then facial tics, and, finally, sudden hand-washing episodes. At the time psychologic treatment was terminated, all such behavior had been absent about four months. No frank seizures have recurred in more than two years.

In Case 2 (N.) interesting variations in the form of seizures occurred. Psychomotor fits replaced "screen spells," and finally grand mal spells tended to replace all other types of seizures. The previously stereotyped form of the boy's bizarre "screen spells" changed, so that new and varied motor and sensory phenomena occurred and alternated with one another.

In Case 3 (R) the impulsive making of abusive telephone calls and uncontrollable giggling disappeared, and grand mal spells persisted; finally, all frank seizure activity disappeared.

It has not been ascertained what characteristic motor or sensory activity is a direct expression of abnormal electrical cerebral discharges, what activity is merely associated with an abnormally discharging brain, and what activity is not related

9. Gibbs, F. A.: Personal communication to the author.

10. Gibbs, F. A.: New Drugs of Value in the Treatment of Epilepsy, Ann. Int. Med. **27**:548, 1947. Toman, J. E. P.; Loewe, S., and Goodman, L. S.: Physiology and Therapy of Convulsive Disorders: The Effect of Anticonvulsant Drugs on Electro-Shock Seizures in Man, Arch. Neurol. & Psychiat. **58**:312, 1947. Toman, J. E. P.: Neuropharmacologic Considerations in Psychic Seizures, Neurology **1**:444, 1951.

to an established paroxysmal cerebral dysrhythmia. No crucial evidence is available to distinguish in any one epileptic patient when a characteristic type of behavior is ictal and when it is nonictal. A recent attempt has been made to differentiate "psychogenic" and "epileptic" seizures in patients with generalized convulsions by a hypnotic-recall technique and electroencephalograms.[11] The assumption is made that if a patient can recall details of his seizure during hypnosis the seizure is "psychogenic"; if he cannot do so, it is "epileptogenic." Such an assumption is unwarranted. The hypnotic-recall technique demonstrates only which seizure phenomena are possible of recall under hypnosis. It does not give information as to which convulsions are epileptic—which are accompanied by paroxysmal or otherwise deviant cerebral electrical discharges. There are many epileptic manifestations, also, in which recall of the convulsive behavior may not be seriously affected, e. g., in many minor seizures, in certain initial seizure phenomena of major seizures,[12] and in Jacksonian and focal convulsions.

Psychologic Conflicts as Precipitants of Seizures.—That external or internal psychologic stress may precipitate an epileptic seizure is generally accepted, but the phenomenon is not well understood or accounted for.

Textbook classifications of the epileptic syndromes have recognized that type of genuine seizure which is triggered by a psychologic or sensory event. These seizures have been labeled "reflex epilepsy" and "affective epilepsy."[13] Various stressful psychologic stimuli are routinely used to elicit experimental seizures in animals whose brains have been traumatized, one standard method being vigorous prodding of the animal with a stick.[14]

Clinical and therapeutic studies of epileptic persons have been reported as showing a relation of psychologic stress to onset of epileptic seizures in some patients.[15] Mittelman [15a] has recently reviewed the theoretical views and clinical evidence relevant to such matters. Ingenious attempts to correlate the arousal of emotional conflict with paroxysmal or abnormal electroencephalographic activity have given suggestive, but not conclusive, evidence that psychologic conflict or stress can, in some persons, initiate epileptic behavior.[15a]

The data collected in the present study are indeed compatible with the view that epileptic seizures and/or behavioral disorders occurring in a patient with epilepsy may be precipitated by an event or events of psychologic nature.

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11. Peterson, D. B.; Sumner, J. W., Jr., and Jones, G. A.: Role of Hypnosis in Differentiation of Epileptic from Convulsive-Like Seizures, Am. J. Psychiat. **107**:428, 1950. Sumner, J. W., Jr.; Cameron, R. R., and Peterson, D. B.: Hypnosis in Differentiation of Epileptic from Convulsive-Like Seizures, Neurology **2**:395, 1952.

12. Penfield, W., and Kristiansen, K.: Epileptic Seizure Patterns: A Study of the Localizing Value of Initial Phenomena in Focal Cortical Seizures, Springfield, Ill., Charles C Thomas, Publisher, 1951, p. 10.

13. Wilson, S. A. K.: Neurology, Baltimore, William Wood & Company, 1940, Vol. 2.

14. Kopeloff, N.; Kopeloff, L. M., and Pacella, B. L.: The Experimental Production of Epilepsy in Animals, in Epilepsy: Psychiatric Aspects of Convulsive Disorders, edited by P. H. Hoch and R. P. Knight, New York, Grune & Stratton, Inc., 1947, p. 163.

15. Clark,[3d] Fremont-Smith, F.: The Influence of Emotion in Precipitating Convulsions: Preliminary Report, Am. J. Psychiat. **13**:717, 1934. Gowers, W. R.: Epilepsy and Other Chronic Convulsive Diseases: Causes, Symptoms, Treatment, Ed. 2, London, J. & A. Churchill, Ltd., 1901. Mittelman.[15a] Pond, D. A.: Psychiatric Aspects of Epilepsy in Children, J. Ment. Sc. **98**:404, 1952.

An attempt will be made to synthesize the common denominators of psychologic events that eventuated in seizures, or seizure-like activity, in these three children. The personal situation, generally the first in a sequence of personal events, that repeatedly led to paroxysmal behavior in these patients may be described as the blocking of any drive or strong emotion from gratification or expression by either an internal, autonomous inhibiting factor or an external agent and/or situation. The aim of the drive whether to get support or protection, to escape a situation, to fight, or to attack apparently made no difference as to its adequacy in activating the chain of events leading to a seizure. The important feature was the blocking of such an aim, or the blocking of the conventional manner of communication of a feeling associated with such an aim.

Other psychiatrically oriented reports on the psychogenesis of epilepsy have tended to single out one impulse, or drive, as the one which was blocked or conflictual, e. g., a need to express anger,[16] desire for sexual activity,[8h] or desire for dependence.[31] In the present investigation the operation of a single specific conflictual drive as the constant psychologic precipitant in epileptic seizures could not be substantiated.

An objection to the concept that any blocked drive or emotion can elicit an epileptic episode in a person so predisposed might be that this concept in no way distinguishes the psychologic conflict leading to an epileptic episode from that reportedly leading to other states of somatic dysfunction, e. g., asthma, hypertension, peptic ulcer, or colitis. Further study of this matter is necessary before final conclusions can be drawn. It is possible, after all, that epileptic children do not vary significantly in the range of psychologic conflicts that can trigger their episodes of somatic dysfunction from children with other recurring episodic bodily dysfunctions.

How do these epileptic children differ from children without symptomatic disease? Is not such a psychologic conflict common in all people? It is acknowledged that such a conflict is probably universal. Two points distinguished these epileptic children from other children in general:

1. Neurophysiologically, their seizure threshold was lower than that of other children. Psychologically, they had a predisposition to paroxysmal, explosive neuromuscular and sensory activity.

2. Their impulses and emotions were more primitive, less mature, than those of other children of comparable age. Consequently, perhaps psychologic conflicts were more overwhelming.

In the present study evidence for the latter point accrued from two sources. One was the clinical judgment of the therapist; the other was the standardized evaluation via psychologic tests. The analysis, by Dr. Samuel Beck, of the Rorschach protocols showed clearly in each child a decided immaturity, in which drives or emotions were poorly integrated with the total personality. These tests revealed, furthermore, a chronic blocking of gratification or expression of motivational needs. In summary, the Rorschach test findings tended to corroborate the clinical finding that the epileptic children studied had special vulnerabilities to the mobilizing of unacceptable drives.

16. Freud, S.: Dostoevski and Parricide (1928), in Collected Papers, London, The Hogarth Press, 1950., Vol. 5, pp. 222. Bartemeier, L. H: Some Observations on Convulsive Disorders in Children, Am. J. Orthopsychiat. **2**:260, 1932.

Effect of Psychotherapy on Epileptic Manifestations.—That reports of psychotherapeutic attempts in the management of epilepsy in children have been few has been noted.[17] Lennox stated:[17a] "I have encountered no convincing reports in the medical literature of successful treatment of epilepsy by psychotherapy." In fact, he cautions, "Formal analysis should not be attempted in a child."

Previous surveys have indicated that roughly 20% of persons whose seizures begin in the first decade of life have remissions during other types of treatment, lasting two years or longer.[18] In the present study, the seizures of two of the children have not yet recurred, during a period of more than two years. The probability of observing two or more two-year remissions in three patients is approximately 1 : 10.

The experience with these epileptic children offers some evidence that psychoanalytic psychotherapy was decisively beneficial in the treatment of their epilepsy. The results do not give evidence that psychotherapy is superior to other forms of treatment, such as anticonvulsant medication. I feel, nevertheless, that it is justifiable to generalize from the findings that psychotherapy judiciously combined with anticonvulsant medication may effect greater reduction in the seizure manifestations of certain patients than the use of anticonvulsant medication alone. Further studies are necessary to determine which epileptic persons may benefit from psychotherapy, and to what extent they can benefit.

In any event, the success of psychologic treatment of these three children is offered as evidence that psychologic, as well as other factors, may play a decisive role in the development of epileptic phenomena.

SUMMARY

1. The seizure frequencies of three epileptic children decreased notably during and after a course of psychotherapy. The seizures of two of the children have not recurred for two years.

2. The form of the ictal manifestations of the children, as well as the seizure frequency, was modified during psychotherapy.

3. The above findings constitute evidence that psychologic factors, as well as other factors, can contribute to the form and frequency of seizures and associated clinical manifestations. Evidence is given which supports the hypothesis that interpersonal events, as well as intrapersonal conflicts, can activate epileptic behavior.

Dr. F. A. Gibbs, Dr. J. P. Toman, and Dr. H. M. Serota interpreted the electroencephalographic records, and Dr. Samuel J. Beck evaluated the Rorschach studies.

17. (*a*) Lennox, W. G.: Science and Seizures: New Light on Epilepsy and Migraine, New York, Harper & Brothers, 1941. (*b*) Kanner, L.: Child Psychiatry, Ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1948.

18. Turner, W. A.: Epilepsy: A Study of the Idiopathic Disease, London, The Macmillan Company, 1907. Of 11 patients of all ages under bromide treatment whose disease began in the first decade of life, remission of two years or more occurred in 19.8%. Lennox, W. G.: Epilepsy, in Nelson New Loose-Leaf Medicine, New York, Thos. Nelson & Sons, 1932, Vol. 6, p. 261. A study of 1,000 case histories of noninstitutionalized epileptic patients of all ages showed that 23% had remissions lasting more than one year. Wilkins, L.: Epilepsy in Childhood: The Incidence of Remissions, J. Pediat. **10**:329, 1937. A study of 200 children, some treated with sedative drugs, some not so treated, showed that 19% had remissions of two years or longer.

STUDIES IN MYASTHENIA GRAVIS

Use of Edrophonium Chloride (Tensilon) in Differentiating Myasthenic from Cholinergic Weakness

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IN THE patient with myasthenia gravis weakness may develop either as an inherent part of the disease or from overtreatment with anticholinesterase. The differentiation of these two types of weakness presents a difficult and serious problem, often unrecognized in the management of the patient with myasthenia gravis. The rapidity with which this weakness may lead to fatal termination justifies the use of the terms "myasthenic crisis" and "cholinergic crisis." When the weakness is extreme and is due to the disease, it is called "myasthenic crisis"; when the weakness is extreme and is due to overtreatment with anticholinesterase, it is called "cholinergic crisis." A method for differentiating these reactions is offered by the edrophonium chloride (Tensilon) test.[1]

Cholinergic crises have become more frequent in recent years, since the advent of a number of organic esters of phosphoric acid derivatives in the treatment of myasthenia gravis. These drugs are diisopropyl fluorophosphate, tetraethylpyrophosphate, and, more recently, octomethylpyrophosphoramide. These alkyl phosphate agents have a very strong anticholinesterase activity, reducing the red-cell and plasma cholinesterase to very low levels. Neostigmine, on the other hand, relieves the weakness of myasthenia gravis, probably by a dual action. Its major action, perhaps similar to that of the alkyl phosphates, is in potentiating the normal method of excitation of the muscle fiber through the inhibition of the cholinesterase. Neostigmine may also act as a direct antagonist to a curare-like blocking substance, whatever its nature, in myasthenia gravis.[2] This action is suggested by the effect of neostigmine on muscle when the cholinesterase has been destroyed by another anticholinesterase compound, diisopropyl fluorophosphate, and by the fact that recovery of the muscular power, after administration of neostigmine, can persist after the serum cholinesterase has returned to the resting level. There is a synergism between the alkyl phosphate compounds and neostigmine, so that in the early

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1. Osserman, K. E., and Kaplan, L. I.: Rapid Diagnostic Test for Myasthenia Gravis: Increased Muscle Strength, Without Fasciculations, After Intravenous Administration of Edrophonium (Tensilon) Chloride, J. A. M. A. **150**:265 (Sept. 27) 1952.

2. Nevins, S., in Feiling, A., Editor: Modern Trends in Neurology, Chapter on Myasthenia Gravis, New York, Paul B. Hoeber, Inc., 1951.

reports [3] of the therapeutic use of these agents it was advised that their combined use was contraindicated, since drug toxicity was easily induced. This toxicity, known as cholinergic crises, may occur also with the use of each drug alone. Despite this synergism, investigators during the past year have been using a combination of neostigmine and octomethylpyrophosphoramide to achieve a better therapeutic result. Very small doses of neostigmine are prescribed to enhance the sustained effect of the alkyl phosphates.[4]

It has long been known that the action of acetylcholine is twofold [5]: a muscarine-like action, on smooth muscle and glands, and a nicotine-like action, on ganglia and striated muscle. The nicotine-like action is also a twofold one: In small doses it is manifested by stimulation of neuromuscular activity; in large doses it is manifested by depression of this activity, and even paralysis. One would expect that acetylcholine would be the drug of choice in the treatment of myasthenia gravis, except for the fact that it is quickly hydrolyzed by the cholinesterases and its effect is therefore transient. It is well known that the myasthenic patient can tolerate much larger doses of acetylcholine and other cholinergic drugs than the normal person. This does not eliminate the possibility of cholinergic toxicity if the dose is too high or if the patient is hypersensitive to these drugs. When anticholinesterase drugs are pushed to toxicity, too much acetylcholine is produced, resulting in neuromuscular block (nicotine-like effect), which causes increased weakness, and even paralysis, of muscle. This results in the cholinergic crisis.

The clinical syndrome of the cholinergic crisis is best seen in those nonmyasthenic patients who have been exposed to the anticholinesterase insecticides. Such cases were first reported by Grob and associates.[6] The patient is extremely weak, often becomes comatose in a short time, and has respiratory difficulty. In a recent review, Grob added to this knowledge of the cholinergic crisis through a description of the systemic effects of nerve gas (anticholinesterase) poisoning.[7] These effects were divided into three types.

1. Muscarine-like effects: These are usually the first to appear and consist of anorexia, nausea, sweating, and epigastric and substernal tightness, with heartburn and eructation. These initial effects are followed by abdominal cramps, increased peristalsis, vomiting, profuse sweating, and dyspnea, with reduction in vital capacity and in maximal breathing capacity.

2. Nicotine-like effects: Shortly after the onset of the moderate, muscarine-like effects, there ensue increased fatigability, mild generalized weakness, involuntary muscular twitchings, scattered fasciculations, and sometimes muscle cramps. Extensive exposure results in severe generalized weakness, including weakness of the muscles of respiration, with respiratory distress. The fasciculations, which usually

3. Rider, J. A., and others: Treatment of Myasthenia Gravis with Octamethyl Pyrophosphoramide, J. A. M. A. **145**:967 (March 3) 1951.

4. Schwab, R. S.: Personal communication to the authors. Eaton, L. M.: Personal communication to the authors.

5. Goldman, A., and Osserman, K. E.: Use of Acetylcholine in the Treatment of Peripheral Vessel Occlusions, with Report of 3 Cases, M. Rec. **139**:579 (June 6) 1934

6. Grob, D.; Garlick, W. L.; Merrill, G. G., and Freimuth, H. C.: Death Due to Parathion, an Anticholinesterase Insecticide, Ann. Int. Med. **31**:899 (Nov.) 1949.

7. Grob, D., and Harvey, A. M.: Effects and Treatment of Nerve Gas Poisoning, Am. J. Med. **14**:52 (Jan.) 1953.

appear first in the eyelids and in the muscles of the face and calf, become generalized. Electromyographic studies show alterations in neuromuscular function, which are attributable to the accumulation of excessive acetylcholine at the motor endplate.

3. Effects on the central nervous system: These include tension, anxiety, extreme nervousness, restlessness, emotional lability, and giddiness. Later, insomnia, with excessive dreaming and occasional nightmares, occurs. If exposure is extensive, headache, tremor, drowsiness, difficulty in concentration, slowness of recall and mental confusion develop. Severe exposure to Parathion (*p*-nitrophenyl diethylthionophosphate, an insecticide) causes ataxia, slurring of speech, coma, areflexia, Cheyne-Stokes respiration, generalized convulsions, and, finally, depression of respiration.

The pathological physiology of the myasthenic crisis must be compared with that of the cholinergic crisis. The fact that neostigmine is an anticholinesterase drug has led to frequent discussion in contemporary literature of two possible abnormalities at the neuromuscular junction in myasthenia gravis, namely, increased cholinesterase activity and diminished production of acetylcholine. Since neostigmine is effective, it is obvious that it would correct both these abnormalities if they in fact existed, but there is no conclusive evidence to suggest that either exists. There is interesting evidence that some abnormal metabolite, a curare-like substance, is present at the neuromuscular junction in myasthenia gravis. Wilson and Stoner [8] have tested on a nerve-muscle preparation the effect of serum withdrawn from patients with myasthenia gravis during occlusion of the circulation, before and after exercise. It produced a curare-like lowering of the height of the contraction to nerve stimulation, with a slight effect (not greater than 25%) before exercise, but a pronounced depression of responses after exercise, amounting in some cases to complete blocking of neuromuscular transmission. Furthermore, no abnormality has yet been found in the true or pseudo cholinesterase content of the blood [9] or muscle [10] in the myasthenic patient. Measurements of the quantitative amount of acetylcholine formed at the neuromuscular junction in myasthenia gravis have not yet been made, but this information will subsequently help to clarify the physiology of this illness. Thus, although the physiologic mechanism in myasthenia gravis is not completely understood, it is different from the changes in the cholinergic crises, even though the weakness exhibited by the patient in the two syndromes may be similar.

METHODS

Recently we reported on the use of edrophonium chloride (Tensilon) as a rapid diagnostic test in myasthenia gravis.[1] The test revealed that normal and psychoneurotic controls exhibited fasciculation [11] of muscles, notably of the orbicularis

8. Wilson, A., and Stoner, H. B.: Myasthenia Gravis: A Consideration of Its Causation in a Study of 14 Cases, Quart. J. Med. **13**:1-18 (June) 1944.

9. Osserman, K. E.: Unpublished data.

10. Wilson, A.; Maw, G. A., and Geoghegan, H.: Cholinesterase Activity of Blood and Muscle in Myasthenia Gravis, Quart. J. Med. **20**:13-19 (Jan.) 1951.

11. Fasciculation is defined as a visible, involuntary contraction or twitching involving a group, bundle, cluster, or fasciculus of muscle fibers.

oculi, without increase in muscle strength. It was also noted that myasthenic patients showed increased muscle strength without fasciculation of muscles when in a basal state (three to four hours after withdrawal of neostigmine). However, in testing our myasthenic patients, we noted that those not in a basal state had reactions which approximated those of the control group. Therefore, it was decided to use the edrophonium test in a group of patients most of whom were being transferred from neostigmine to octomethylpyrophosphoramide in order that we might determine the optimal dose of the latter drug. We subsequently found that the edrophonium test could be used to differentiate cholinergic and myasthenic weakness.

Responses to Edrophonium Test

	Myasthenic	Adequate	Cholinergic
Muscle strength	Increased	No change	Decreased
Ptosis			
Diplopia			
Dysphonia			
Dysphagia			
Dysarthria			
Respiration			
Limb strength			
Fasciculations	Absent	Present or absent	Present or absent
Orbicularis oculi			
Facial muscles			
Limb muscles			
Side-reactions	Absent	Minimal	Severe
Lacrimation			
Diaphoresis			
Salivation			
Abdominal cramps			
Nausea			
Vomiting			
Diarrhea			

Twelve patients with known myasthenia gravis served as the basis for this study. All had been admitted to the wards of the Mount Sinai Hospital for various reasons and were followed prior to and after discharge from the myasthenia gravis clinic. Their ages varied from 18 to 48 years. Seven were females, and five were males. Nine had been admitted to the wards for transfer from neostigmine to octomethylpyrophosphoramide. The results of the transfer to the latter will be reported subsequently.[12] These patients had daily red-cell cholinesterase studies. They were also given daily 1 cc. (10 mg.) of edrophonium chloride intravenously. Within 30 seconds to 2 minutes patients exhibited the effects, which wore off within the next few minutes. The effects noted were (1) increase or decrease in muscle strength, (2) presence or absence of fasciculations, (3) presence or absence of side-reactions, (4) the eye-closure phenomenon, which may or may not be present.[1]

RESULTS

Although our experience with the use of the edrophonium test as a guide to the management of myasthenia gravis is limited, the responses appeared to fall into clearly defined groupings in this series of patients. It soon became evident that the

12. Osserman, K. E., and Kaplan, L. I.: Studies in Myasthenia Gravis: Therapy with Octomethylpyrophosphoramide, to be published.

time relation between the edrophonium test and the dose of previous medication was an important factor which had to be determined. An edrophonium test was performed in the basal state; then a dose of anticholinesterase was given, and subsequently hourly edrophonium tests were performed. The results of these experiments will be reported separately.[13] Certain conclusions were evident with regard to the optimal time for the performance of the edrophonium test to determine adequacy of treatment: 1. The best time to perform the test in relation to the last dose of octomethylpyrophosphoramide is 12 hours. 2. The best time to perform the edrophonium test in relation to the last dose of neostigmine (either the bromide or the methylsulfate salt) is two hours.

Response to Edrophonium Test in Inadequately Treated Myasthenic Patients (Myasthenic Reaction).—Six of the patients while being transferred from neostigmine to octomethylpyrophosphoramide therapy appeared to be suffering from inadequate treatment of their underlying myasthenia gravis. The responses to the edrophonium test before their transfer to octomethylpyrophosphoramide therapy showed that all exhibited increasing strength without fasciculations and without side-reactions. As neostigmine was withdrawn and before octomethylpyrophosphoramide therapy became effective, the responses to the edrophonium test revealed the same reaction as aforenoted, with even further increase in strength and a sense of well-being on the part of the patient.

There were three other patients in this series who revealed inadequate therapy of their myasthenia gravis, due, respectively, to intercurrent infection, a malignant thymoma, and peptic ulcer. It was impossible to control the weakness of the patient with malignant thymoma. In spite of large doses of neostigmine and subsequent transfer to octomethylpyrophosphoramide, her responses to the edrophonium test persistently revealed a myasthenic type of reaction. She had a fulminating course and died three months after onset of symptoms.

Response to Edrophonium Test in Adequately Treated Myasthenic Patients.—In eight of the preceding patients the responses of the edrophonium test revealed the adequacy of their treatment in the following manner: As anticholinesterase therapy became effective, the strength of the patient increased, so that there was little increase in strength when a test with edrophonium was performed. In two patients, minimal fasciculations, lasting but seconds, could be observed in the orbicularis oculi. There was a slight increase in the incidence of side-reactions.

Edrophonium Test in Overtreated Myasthenic Patients (Cholinergic Reaction).—Three of the patients had cholinergic crises, caused by the overtreatment of their myasthenia gravis with anticholinesterase therapy. When overtreatment occurs, the edrophonium test reveals transiently increased muscle weakness, rather than increasing strength. This is especially true in respiratory weakness. In this response the patient complains momentarily of increased fatigability. Fasciculations may or may not occur; they were observed in two patients and were absent in the third. However, much severer side-reactions were observed.

An example of the cholinergic reaction was the case of a white woman aged 39, known to have myasthenia of three years' duration, who required 105 mg. of neostigmine bromide a day,

13. Osserman, K. E.; Kaplan, L. I., and Besson, G.: Studies in Myasthenia Gravis: Endrophonium Chloride (Tensilon) Test as a New Approach to Management, J. Mt. Sinai Hosp. **20**:3 (Sept.-Oct.) 1953.

with an occasional addition of 1 mg. of neostigmine methylsulfate given subcutaneously. She was a highly neurotic person, who had many emotional problems in her home and business life. At time of stress, she would become weak and suffer severe headaches. She would increase her dose of neostigmine to the point of experiencing increasing lassitude, headache, and depression. The edrophonium tests performed at these times revealed marked fasciculations of the orbicularis oculi, increased lacrimation, diaphoresis, abdominal cramps, and the eye-closure phenomenon. Neostigmine therapy was discontinued for 24 hours and reinstituted in a dosage of 15 mg. three times a day. Daily edrophonium tests were performed, and she was finally stabilized at her usual dose, of 105 mg. of neostigmine bromide a day. Her response to the edrophonium test when she was stabilized was that of a patient with adequately treated myasthenia. When this patient faces environmental difficulties, she tends to increase her daily dose of neostigmine and must constantly be advised against this procedure.

COMMENT

In the treatment of myasthenia gravis it is important to differentiate between the weakness of the disease and the weakness caused by overtreatment with anticholinesterase. The former in severe form is called the "myasthenic crisis"; the latter, the "cholinergic crisis." It is difficult to make this differentiation clinically, so that many physicians, and most patients, are not fully aware of the cholinergic crisis. This clinical problem has previously been pointed out by Wilson and associates.[14]

Attention to the various aspects of the patient's history may be helpful in determining the nature of this weakness. If the weakness develops after infection, cessation of medication, trauma, or emotional problems, it is likely to be of myasthenic origin. This situation can be compared with that of the diabetic who, on the same diet and dose of insulin, has his disease get out of control owing to the same factors. When a patient on apparently adequate anticholinesterase therapy, either neostigmine or octomethylpyrophosphoramide, or a combination of the two drugs, has increasing weakness without one of the aforementioned causes, and when, as drug therapy is increased, even more weakness develops, a cholinergic origin must be suspected, and one must discontinue administration of the anticholinesterase compounds. In the latter situation, the patient may also exhibit diaphoresis, diarrhea, and increasing abdominal discomfort, which are symptoms of overdosage with the anticholinesterase compounds.

We have used the edrophonium test as a means of differentiating the cause of weakness in patients with myasthenia gravis under treatment. The results of this test, when properly interpreted, were found to be a sensitive index to the effectiveness of therapy. There were three types of responses: (1) that of the inadequately treated patient, or the myasthenic reaction, in which there was evidence of insufficient anticholinesterase therapy; (2) that of the adequately treated patient, showing that the patient was receiving sufficient anticholinesterase therapy, and (3) that of the overtreated patient, or the cholinergic reaction, in which there was evidence that too much anticholinesterase therapy was prescribed.

Patients during the first few days of their transfer to octomethylpyrophosporamide (before the cholinesterase value falls to low levels) show the typical myasthenic response to the edrophonium test. As the octomethylpyrophosphoramide

14. Wilson, C. W.; Williams, J. P., and Miller, D. H.: Hazard of Cholinergic Crisis During Treatment of Myasthenia Gravis with Octamethyl Pyrophosphoramide, Ann. Int. Med. **37**:574 (Sept.) 1952.

doses reached therapeutically effective levels, there was little increase in muscle strength with the edrophonium test. When overtreatment with anticholinesterase drugs occurred, the edrophonium test revealed increasing muscle weakness and generalized fatigability. If respiratory weakness was present, it is unrelieved. Fasciculations might or might not occur. However, increasing side-reactions were observed. These side-reactions might become the dominant part of the response to the edrophonium test.

In two cases the edrophonium test was helpful in determining the optimal neostigmine dose before operation. The patients were prepared for surgery by determining the amount of neostigmine methylsulfate given prior to operation to keep them in good strength. The results with the edrophonium test prevented overdosage with neostigmine.

The edrophonium test was of real value in making the differential diagnosis of crisis. In three patients the edrophonium test clearly demonstrated that overdosage, i. e., a cholinergic crisis, was the major difficulty. In one of these patients, unfortunately, the result of the edrophonium test was not properly interpreted and further anticholinesterase therapy was given, resulting in respiratory failure and death. This was our first experience with the use of the edrophonium test in the cholinergic crisis, and we overemphasized the absence of fasciculations in its interpretation and did not pay enough attention to the increasing side-reactions and the weakness produced by the test. The second patient had marked respiratory weakness, and the edrophonium test revealed a cholinergic response. The patient was given 1/50 grain (1.2 mg.) of atropine sulfate intravenously, and use of neostigmine was stopped. He responded to this therapy. In the third patient showing cholinergic responses, neostigmine administration was stopped and the condition improved.

In three other patients the edrophonium test revealed inadequate therapy of the myasthenia gravis, caused by increased resistance on the part of patients, due to the presence, respectively, of intercurrent infection, a gastric ulcer, and a malignant thymoma. The first two were treated for their secondary conditions, and for their myasthenia they received increased amounts of neostigmine. The third patient had a fulminating course and died of her malignant thymoma.

Prior to the introduction of the edrophonium test, the diagnosis of cholinergic crises could be made only by clinical judgment. The test appears to differentiate clearly myasthenic and cholinergic weakness. We recommend that it be performed routinely whenever this problem arises, particularly if respiratory distress is present. The test is very simple to perform, requiring only a few minutes. The observer can make the differential diagnosis at the bedside. Edrophonium is rapidly excreted from the body (within 60 minutes at the most),[15] and there is little danger of its adding to a cholinergic crisis.

SUMMARY

Myasthenic and cholinergic crises in myasthenia gravis are described and discussed. The crises are characterized by extreme weakness, which may be an inherent part of the disease or be due to overtreatment with anticholinesterase.

15. Westerberg, M. R.; Magee, K. R., and Shideman, F. E.: Effect of 3-Hydroxy Phenyldimethylethylammonium Chloride (Tensilon) in Myasthenia Gravis, Univ. Michigan M. Bull. **17**:311 (Sept.) 1951.

The clinical and pathophysiological features of the two types of crises are described.

The use of edrophonium chloride (Tensilon), 1 cc. (10 mg.) given intravenously, is described as a test to differentiate myasthenic from cholinergic weakness and crisis. The optimal time in which to perform the edrophonium test is 12 hours after the last dose of octomethylpyrophosphoramide and two hours after the last dose of neostigmine.

Three types of response to the edrophonium test were found in this series of 12 patients with myasthenia gravis: (*a*) the myasthenic reaction, in inadequately treated myasthenic patients, characterized by increased muscle strength without fasciculations (nine patients); (*b*) the response in adequately treated myasthenic patients, showing no change in muscle strength, with or without fasciculations (eight of the preceding patients after treatment); (*c*) the "cholinergic reaction," in overtreated myasthenic patients, showing decreased muscle strength with or without fasciculations and severe side-reactions (three patients).

The edrophonium test is rapid, can be performed at the bedside, and is without danger to the patient in our experience.

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EVIDENCE FOR SUPPRESSION FROM THE TEMPORAL LOBE IN THE MONKEY

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DUSSER de Barenne and McCulloch,[1] in 1939, described the phenomenon of cortical suppression following the application of strychnine or electrical stimulation to certain regions of the central cortex. They found after such stimulation a decrease in electrical activities in other areas of the central cortex and also a decrease in the function of the specific areas of the cortex. Somewhat similar phenomena have been described in the various forms of extinction and of spreading depressions of Leão.[2] Dusser de Barenne, Garol, and McCulloch[3] described particular areas of the cortex from which the suppression response could be elicited. They originally described Areas 4s, 2s, 8s, and 19s, and, later, Area 24, on the medial aspect of the hemisphere. But there has been some disagreement with their views. Marshall and Essig[4] maintained that the suppressor areas do not exist as such and that Dusser de Barenne and McCulloch were measuring changes induced by drying of the cortex or changes in temperature, and therefore like the changes of the spreading depression described by Leão. They were of the opinion, furthermore, that the various types of depression could be elicited more easily after prolonged experimenting. Other investigators[5] believe that suppressor cortex does exist but that it is not gathered in the clear-cut bands or areas described by Dusser de Barenne and McCulloch, but, rather, that there are points of cortex from which suppressor response can be elicited.

These suppressor areas are in juxtaposition to the cortex serving a particular function. For example, Area 4s of the cortex is near the motor cortex; Area 2s is part of the somatosensory region of the cortex; Area 19s is identifiable with the

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1. Dusser de Barenne, J. G., and McCulloch, W. S.: Suppression of Motor Responses upon Stimulation of Area 4-s of the Cerebral Cortex, Am. J. Physiol. **126**:482, 1939

2. Leão, A. A. P.: Spreading Depression of Activity in the Cerebral Cortex, J. Neurophysiol. **7**:359, 1944.

3. Dusser de Barenne, J. G.; Garol, H. W., and McCulloch, W. S.: Physiological Neuronography of the Cortico-Striatal Connections, A. Res. Nerv. & Ment. Dis., Proc. **21**:246, 1942.

4. Marshall, W. H., and Essig, C. F.: Relation of Air Exposure of Cortex to Spreading Depression of Leão, J. Neurophysiol. **14**:265, 1951.

5. Walker, A. E.: Personal communication to the authors. Forster, F. M.: Unpublished data.

visual cortex; Area 8s is just posterior to the prefrontal lobes, and Area 24, on the medial aspect of the hemisphere, is a part of the cingular gyrus region. It would seem, therefore, that with each functional region of cortex there should be a suppressor area, or region, depending upon the terminology one wishes to use. It is obvious that if suppressor areas are present elsewhere, there should also be suppressor areas in the temporal lobe, in association with the auditory cortex. The present investigation was undertaken to prove or disprove the presence of suppressor areas or regions in the temporal lobe of the Macacus mulattus.

MATERIAL AND METHODS

Experiments were carried out on 31 Macacus mulattus monkeys. Preliminary experiments were carried out on cats merely to test methods and techniques, but data from these experiments were not included in the results because of the vast difference in architecture, and even gross arrangement, of the cat and primate temporal lobes. The anesthetic used was Dial (5,5-diallylbarbituric acid)-urethan.[6] This was administered in a dose of 0.45 mg. per kilogram of body weight, one-half the dose being injected intraperitoneally and one-half intramuscularly; during the actual operative phase of the experimental procedure, this anesthetic was supplemented by intramuscular injection of pentobarbital in a dose of 10 mg. per kilogram. With this procedure, the actual experiments were carried out with the animals under very light anesthesia.

All electrocorticograms were taken with a six-channel ink-writing electroencephalograph. The electrodes were cotton wick held by a Grass electrode holder. Visual stimulation was carried out by means of a stroboscope. To this was attached a sound stimulator, which was so constructed that with each flash of light a clicking sound was transmitted through a loud speaker, the amplitude of which could be changed. Electrodes were placed over other areas of the cortex—over frontal, parietal, and occipital lobes for control recordings—and Area 17 was determined by its electrical response to the stroboscope. The visual cortex was easily isolated in all but two monkeys. The acoustic cortex was found with great difficulty, and only in five monkeys. It is believed that this occurs because the acoustic cortex is buried in the fissure of Sylvius, and for our purposes we did not wish to damage the cortex of the brain by looking further for it. All the electrodes were moistened with isotonic saline solution, and the brain was kept moist with isotonic saline at a temperature of 37 C. At no time was the hemisphere permitted to dry. All recordings used in these experiments were carried out within 12 hours after exposure of the hemisphere. All were bipolar, from electrodes not more than 8 mm., and usually 3 mm., apart. Both strychnine and electrical stimulation were employed to determine whether or not a particular area of cortex was suppressor in function. Whenever electrical stimulation gave rise to what appeared to be suppression, this observation was checked by strychninization.

Whether or not suppression was obtained at a particular point was decided by (*a*) the presence or absence of periods of decrease in ampltiude and frequency of the brain waves from all the areas of the cortex and/or (*b*) a decrease in the physiologic response of the visual cortex to visual stimuli (stroboscopic) and (*c*), in the few experiments in which it was possible, a depression in the activity evoked from the acoustic cortex by sound stimuli. The strychnine was applied on filter-paper pledgets 1 mm. square. These pledgets were soaked in a saturated solution of strychnine and applied gently with forceps, so as not to rub the cortex. They were removed as soon as adequate strychnine spiking occurred. Electrical stimulation was by means of a Grass stimulator with a frequency of 50 cps, a voltage of 2 to 4, and a duration of 0.8 to 1.2 seconds.

RESULTS

These experiments demonstrated a suppressor response from the temporal lobe of Macacus mulattus. Under the conditions of these experiments, electrical and strychnine stimulation produced a decrease in electrical activity of the cerebral

6. Dial with urethan was supplied by Ciba Pharmaceutical Products, Inc.

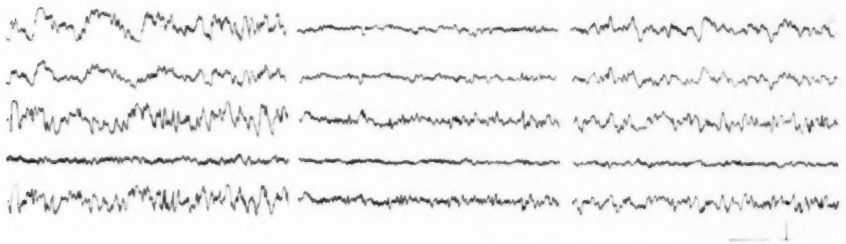

Fig. 1.—The upper two tracings are scalp recordings from the right, unexposed hemisphere. The lower three tracings are corticograms from the exposed (left) hemisphere, the third being from the frontal lobe, the fourth from the suppressor region of the temporal lobe, and the fifth from the temporal lobe, posterior to the suppressor region. The series of tracings on the left were taken before electrical stimulation of the suppressor region; the middle set were taken five minutes after electrical stimulation, revealing decrease in electrical activity; the tracings at the right show return of electrical activity 20 minutes later. In this Figure, and in Figures 2 and 3, the horizontal marker indicates 1 second; the vertical marker, 50 volts.

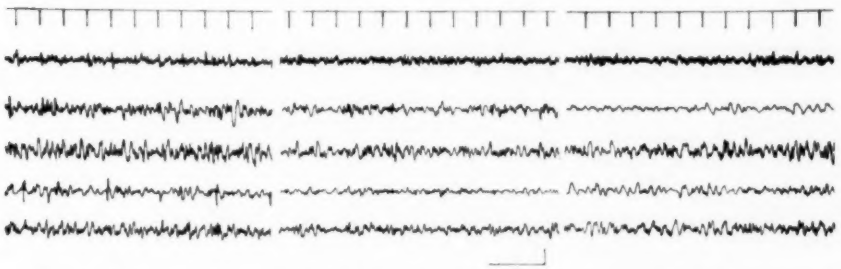

Fig. 2.—The top tracing records stroboscopic stimuli. The second tracing is from exposed Area 17; the third, from the frontal lobe; the fourth, from the anterior temporal tip; the fifth, from the suppressor region of the temporal lobe, and the sixth, from the posterior temporal lobe. Tracings at the left show strychnine firing of the suppressor region and were taken before suppression occurred elsewhere. Note that the degree of suppression is not equal in all channels at the same time.

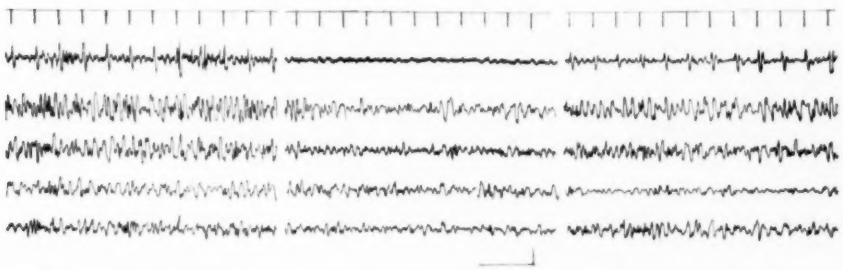

Fig. 3.—The electrode placement was that used in Figure 2. Tracings at the left are controls; tracings in the center were taken three minutes after electrical stimulation of the suppressor region, and those on the right, 20 minutes later. Note suppression of photic responses from the visual cortex.

cortex (Figs. 1 to 3), a decrease in the response of the visual cortex to stroboscopic stimuli, and, when the monkeys were active or restless, a decrease in voluntary activity. These phenomena appeared between 3 and 30 minutes, and usually within 20 minutes, after electrical stimulation. The suppressor response frequently appeared in waves, two, or rarely three, episodes of suppression occurring after a single stimulation. Each episode of suppression lasted from one to five minutes. The suppression of cortical electrical activity did not always sweep the entire cortex

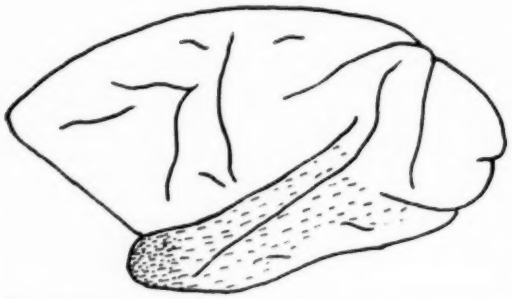

Fig. 4.—Points on the temporal lobe from which suppression was obtained.

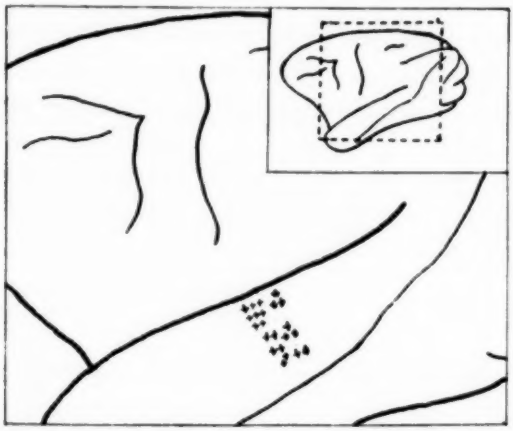

Fig. 5.—Points on the temporal lobe from which suppressor responses could not be obtained.

simultaneously, but appeared in random fashion, decreasing the activity recorded in one or more of the other regions.

The suppressor responses were elicited from the first temporal fissure near the base of the Rolandic fissure (Fig. 4). The experiments were carried out systematically, beginning with the temporal tip and working posteriorly. The temporal tip received particular study. No suppressor response could be elicited from the anterior portion of the first temporal gyrus (Fig. 5). In two of the earlier experiments the temporal tips were traumatized during exposure. Over these traumatized regions, mechanical stimulation, as outlined, evoked suppression. No suppres-

sor responses were evoked from the superior bank of the Sylvian fissure or from the second temporal convolution.

Figures 4 and 5 present the results of all stimuli. Figure 5 shows the areas of stimulation which failed to produce suppression, while Figure 4 presents the areas of stimulation which resulted in suppression. All evidences of suppression were obtained within a particular region of the first temporal convolution, near the base of the Rolandic fissure. This was the only region from which actual suppression was obtained.

From a comparison of Figures 4 and 5, it is apparent that negative responses were obtained from the same region as were positive responses. Two explanations are possible: First, that the suppressor area, if it exists as such, varies in location in different animals, and, second, that suppressor cortex does not constitute an area but, rather, consists of points. Figure 6 presents the data from an experiment on a macaque. In this experiment, the suppressor points were found at the points indicated by plus signs. In the center of each of these points was another point from

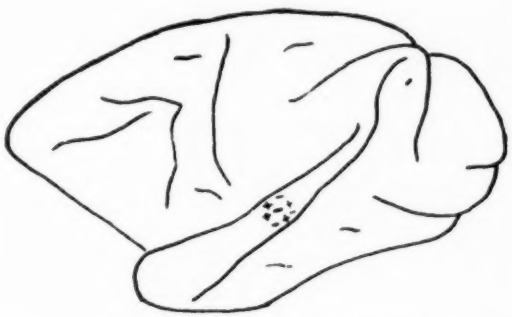

Fig. 6.—Suppressor points and nonsuppressor points determined in a single experiment.

which no suppression could be elicited, either by electrical or by strychnine stimulation. This is indicated by a minus sign.

The suppressor response was, therefore, elicited from points rather than from a discrete area of cortex. These points of suppression were grouped in a region, with a tendency for the stronger suppressor points to be near the center and the weaker suppressor points to be at the periphery; nevertheless, a random representation existed, with some points of no suppression definitely within the region.

CONCLUSIONS

From the foregoing data it is concluded that suppressor points exist in the temporal lobe. There is no evidence for a discrete suppressor area; rather the results indicate a region which includes both suppressor points and points of no suppression. This finding indicates that the auditory cortex of the temporal lobe is similar to other cortical regions of known specific function. The absence of suppressor responses from the temporal lobe would require considerable explanation, since other functional units of cortex are accompanied by suppressor cortex.

The absence of a clearly defined area of suppression in the temporal lobe and the present tendency away from the concept of discrete suppressor areas elsewhere

raise the possibility of a new concept of suppressor cortex. The points of suppression are not unlike the points in motor and premotor cortex which on stimulation yield alterations in pulse rate and blood pressure, or the pupillodilation and constriction responses from Area 8. The greatest representation of autonomic functions within the central nervous system is the hypothalamus; by comparison, cortically elicited alterations are weak. The suppressor, or inhibitory, and the facilitatory responses from the reticular substance are comparable to the autonomic responses from the hypothalamus, while cortical suppression is comparable to cortical autonomic responses. Viewed from the standpoint of encephalization, suppression, and perhaps facilitation, is a function not yet clearly within the confines of cortical function, and is best served by subcortical regions.

The clinical significance of these suppressor responses is not yet definite. It is quite possible they may play a role in temporal lobe seizures, particularly psychomotor seizures. Investigations in progress are directed toward this problem.

SUMMARY

Suppressor responses can be elicited from points of the temporal lobe cortex of the Macacus mulattus. These points are in the first temporal convolution near the base of the Sylvian fissure.

ANGIOGRAPHIC CHANGES IN SUDDEN AND SEVERE HERNIATION OF BRAIN STEM THROUGH TENTORIAL INCISURE

Report of Five Cases

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IT IS NOT an uncommon occurrence in carotid angiography that after the first injection of contrast medium nonfilling or incomplete filling of the cerebral vascular tree is found. Thus, if the opaque medium is visible at all, only the internal carotid artery may be filled, while its terminal branches, that is, the middle and anterior cerebral arteries, cannot be visualized. This is true even though no major obstructions can be disclosed and the time of exposure remains unchanged. Repeated injections into the same artery, and injections into the opposite one, will usually result in an angiographic demonstration of the entire vascular tree. At times, however, partial filling will ensue even on repeated injections, resulting in a series of films apparently indicating a holding up of the contrast medium due to obliteration of the internal artery.

Within the current year, however, five cases have come under our observation that may shed light upon the physiopathological processes involved in what will be shown to be quasiobliterations of the cerebral arteries. These were five cases of an intracranial space-taking lesion in which signs were revealed in the angiogram of a holding of the medium in the internal carotid artery, although in no case was an anatomical obstruction of the artery found at a later stage. The nature of the lesions varied widely. Common to them all, however, was the fact that the space-taking lesion had led to a sudden rise in the supratentorial intracranial pressure, and that at the time of angiography signs were present of severe herniation of the brain stem through the incisura tentorii, with ensuing severe disorders of consciousness and of circulation, together with respiratory embarrassment, even increasing to cessation of respiration.

The case records will be summarized with particular regard to points relevant to the subsequent discussion.

REPORT OF CASES

CASE 1.—*Large cyst in the left cerebellar hemisphere in a man aged 33.*

On Aug. 8, 1951, the patient was transferred to the department of neurosurgery from the department of neurology of this institution. For about a year he had complained of attacks of severe fronto-occipital headache, precipitated by stooping and, later, by even the slightest move-

From the State Department of Neurosurgery, City Hospital and University of Aarhus.
Prof. R. Malmros gave us free access to the case records on which this study was based.

ment of the head. Eventually, nausea, vomiting, and diplopia supervened. During his stay in the department of neurology mild blurring of the optic disk was found on either side. At times he was mildly somnolent. The systolic blood pressure varied from 160 to 110 mm., and the diastolic pressure, from 125 to 80 mm. On Aug. 25, lumbar puncture revealed a spinal fluid pressure of 260 mm. of water, which decreased rather abruptly to 170 mm. after 5 ml. of fluid was removed. During this procedure he complained of aggravation of headache and giddiness. The spinal fluid showed a mild increase in the protein content. On the day of admission to this department he had a sudden and severe aggravation of headache, associated with stiffness of the neck and vomiting. One hour later, he suddenly lost consciousness, his face became flushed and cyanotic, respiration became embarrassed and irregular, and eventually apnea developed. On admission he was unconscious; artificial respiration had been administered for 15 minutes. Endotracheal intubation was immediately performed, and artificial respiration with oxygen exclusively was continued.

On examination he was found to be comatose; there was complete absence of muscular tone, with abolition of the deep reflexes. The corneal reflexes could not be elicited. The pupils were dilated and did not react to light. The optic disks showed mild edema. The pulse was small and weak. The blood pressure was 130 systolic and 80 diastolic. Lumbar puncture revealed a spinal fluid pressure of 100 mm. of water. The fluid was clear and colorless. A bilateral percutaneous carotid angiographic examination was immediately performed. Five injections of contrast medium were made on the left and three on the right side. In all films there was an intense filling of the common carotid artery and the internal and external carotid arteries. But in no instance was there normal filling of the anterior or middle cerebral arteries. After one injection into the left common carotid artery the contrast medium had passed about 15 mm. upward, into the intracranial portion of the internal carotid artery. The actual time of exposure corresponded to the usual cerebral arterial phase. At the same time there was abundant filling of the branches of the external carotid artery. Exposure, after the same injection, corresponding to the usual cerebral venous phase, showed that the contrast medium had advanced about 5 mm. farther upward into the carotid siphon, without entering the middle or the anterior cerebral arteries. At this stage there was no filling of the arteries of the external carotid artery, but a dense filling of the diploic veins of the skull was distinctly visible. After another injection into the left common carotid artery, the contrast medium had passed on as far as to the distal part of the carotid siphon, and small amounts were visible for about 10 mm. in the contiguous parts of the middle and anterior cerebral arteries. All these measurements were made in the lateral films, that is, planimetrically; consequently, they cannot be assumed to reflect the actual distances passed by the contrast medium. On the right the maximum distance of filling, from the entrance of the internal carotid artery to the cranial cavity, was measured to about 20 mm.

During this procedure, which lasted about an hour, the patient's condition became worse. the systolic blood pressure fell to 70 mm. of water, and during the following hours the blood pressure became unmeasurable. Despite continued artificial respiration, with administration of oxygen, he became increasingly cyanotic and died after 21 hours.

Autopsy revealed a large cyst, degenerative in nature, in the left cerebellar hemisphere; it bulged into the fourth ventricle, which had become obliterated. The cerebral aqueduct and the third and the two lateral ventricles were the site of a prominent dilatation; the gyri of the cerebral hemispheres were flattened, and a cerebellar pressure cone was disclosed. Thorough examination of the internal carotid arteries, the middle and anterior cerebral arteries, and the basilar artery and its branches disclosed no intravascular or extravascular abnormalities.

CASE 2.—*Bilateral malignant glioma in the motor and premotor regions, involving the corpus callosum, in a man aged 43.*

One month before entrance to this hospital, he had complained of a sudden violent headache in the neck; after several hours this was followed by a generalized convulsive seizure, associated with unconsciousness. After coming to, he was in a constant state of disorientation and confusion. A lumbar puncture made in his county hospital revealed a spinal fluid pressure of 250 mm. of water. On his admission, Jan. 21, 1952, to this department, his mental state was unchanged. He was disoriented, somnolent, and at times mildly euphoric. Examination showed bilateral loss of hearing and bilateral choking of the optic disk, with marked engorgement of

the veins. The blood pressure was 155 systolic and 110 diastolic. Angiograms made on Jan. 24, after injection into the right common carotid artery, showed questionable signs of a malignant growth in the upper premotor region on the right. On Jan. 25, ventriculograms were made. After the left occipital horn was tapped, the supratentorial pressure was found to be 180 mm. of water. Only a few drops of fluid were removed from the left occipital horn, while 57 ml. of yellowish fluid was let out from the right. At that time the patient was in a state of unrest. The films showed no air in the ventricles, but the subarachnoid space was well filled. An angiographic study of the left carotid system was then decided upon. Because of his incessant unrest, general anesthesia was necessitated. During the initial phase of induction a series of "brain stem fits" developed, with pronounced spasm in extension of the two lower limbs and spasm in adduction-pronation-flexion of the two upper extremities. Despite four injections of contrast medium and delayed exposure, there was only filling of the internal and external carotid arteries. No contrast medium was seen in the middle and anterior cerebral arteries. In one film the arterial shadow could be traced up to the base of the skull. In two additional films the contrast medium had passed on into the intracranial cavity, up to a distance of 2 in. (5 cm.) from the internal opening of the carotid canal. During the angiographic procedure no hypertonic fits were observed, and in the last phase the blood pressure was 135 systolic and 80 diastolic.

Immediately after the angiographic study the left occipital horn was tapped. The supratentorial pressure ranged from 1,140 mm. to a maximum of 1,240 mm. of water. After air had been injected into the ventricle, a tumor shadow was disclosed in the ventriculograms, bulging into the central portion of the left lateral ventricle from above, in the neighborhood of the foramen of Monro, and leading to almost complete blocking. A diagnosis of bilateral malignant glioma was made. A possible operation was deferred, since it became clear that the chance of successful surgical intervention was slight.

During the subsequent days the blood pressure was slightly increased. There was a continuously changing muscular tone, and the patient remained somnolent and confused.

On Jan. 28, angiographic study of the left carotid system was repeated. This was made with local anesthesia, and without difficulty. The internal carotid and the anterior and middle cerebral arteries were all satisfactorily filled in the arteriogram. A roundish patch of delicate abnormal vessels was seen in the region just above the central portion of the lateral ventricle, corresponding exactly to the abnormal shadow disclosed in the ventriculograms. The aforementioned diagnosis was regarded as corroborated, and surgical intervention was judged futile. He died on Jan. 31.

Autopsy disclosed a large multicellular glioblastoma involving the septum pellucidum, the corpus callosum, and the motor and premotor regions of both hemispheres. The central portion of the two lateral ventricles was almost obliterated, and, even though the third ventricle remained unaffected, the almost complete obliteration included the two foramens of Monro.

CASE 3.—*Intraventricular hemorrhage originating in the right corpus striatum in a woman aged 55.*

For at least eight years the patient had suffered from mitral stenosis. Two and one-half hours before admission to this department she suddenly lost consciousness and fell; there was no injury to the head. Powerlessness in the left limbs was noted immediately after the onset.

On admission she was comatose; there was mild cyanosis; respiration was greatly embarrassed. The corneal reflexes were elicitable only with difficulty. The pupils were slightly dilated and did not react to light. Spasm in extension and pronation was observed to occur intermittently in the two upper limbs; between attacks the muscular tension was relaxed. The phenomenon was more pronounced in the left arm. In the two lower limbs a constant spasm in extension was noted. There was a bilateral extensor plantar response. The optic disks were choked, and the veins were engorged. The systolic blood pressure was 240 mm.; the pulse was irregular, with a rate of 64 a minute. An electrocardiogram showed dysrhythmia, with irregular, abnormal, and continuously changing ventricular complexes. During examination apnea developed. An endotracheal intubation was made, and large amounts of mucus and some stomach contents were aspirated from the airway.

Bilateral angiographic study with injection into the common carotid artery showed filling of the right internal carotid artery up to the internal opening of the carotid canal in the first

film, that is, the exposure corresponding to the cerebral arterial phase. In the second film, corresponding to the cerebral capillary and initial venous phases, the contrast medium had passed on for a distance of about 2 in. up to a point just posterior to the anterior clinoid process. On the left the contrast medium had passed on to the base of the skull but no farther. On both sides this incomplete filling of the internal carotid system coincided with a complete filling of the external carotid artery and its branches. During angiographic study the systolic blood pressure was 70 mm. Hg.

Immediately after the angiographic study a lumbar puncture was done. The spinal fluid pressure was 225 mm. of water. About 1 ml. of sanguineous fluid was removed.

Despite continuous artificial respiration, the patient died, nine hours after admission.

Autopsy disclosed a prominent tentorial pressure cone, with deep grooves impressed on the mesial part of the undersurface of the two temporal lobes. There was also a pronounced cerebellar pressure cone. The fourth ventricle was the seat of mild dilatation. The third ventricle and the right lateral ventricle were filled with large clots. The hemorrhage originated in the right corpus striatum.

CASE 4.—*Intraventricular hemorrhage originating in the basal ganglia on the left in a man aged 22.*

The patient, 17 days before admission, had sustained a severe injury to the head. This was unassociated with disorders of consciousness, but during the following fortnight he was incapacitated because of headache.

Six hours before his admission to this department there was a sudden and violent recurrence of the headache, associated with giddiness and vomiting. Fifteen minutes after the onset he lost consciousness.

On admission he was comatose and cyanotic. Respiration was irregular and superficial. There were signs of pulmonary edema. Endotracheal intubation was performed immediately. Mucus was aspirated from the airway, and oxygen was administered. At that stage the systolic blood pressure was 210 mm. Hg. The pulse rate was 84, and the respiration rate 18, a minute; the temperature was 93 F. (34 C.). The corneal reflexes were weak. The eyes were slightly divergent. The fundi showed blurring of the optic disks and venous engorgement. There was generalized loss of muscular tone. Deep reflexes were unelicitable in either upper limb; the patellar jerks were normal, and the ankle jerks were diminished. Lumbar puncture showed a spinal fluid pressure of 700 to 800 mm. of water. The spinal fluid contained blood. At that stage the systolic blood pressure was raised to 250 mm. Hg; the pulse rate was 164, and the respiration rate 12, a minute.

Just before the patient was ready for angiography, apnea developed. Consequently, burr holes were made in the occipital region bilaterally, and the occipital horn was tapped on either side. The supratentorial pressure was 200 mm. of water, increasing to a maximum of 250 mm. Fresh blood was disclosed in the ventricular fluid. A small rubber tube was placed in each lateral ventricle. Repeated measurement of systolic blood pressure showed a fall to 120 mm. Hg; the pulse rate was 128 a minute, and the patient remained in a state of apnea.

Angiograms, made after injection into the two common carotid arteries, showed filling of the extracranial and cranial divisions of the internal carotid artery, while none was seen in the intracranial portion. From below upward the contrast medium tapered slightly away. In one film only was the intracranial portion of the internal carotid artery filled for nearly an inch (2.5 cm.). In most films the partial fillings of the internal carotid artery coincided with an abundant filling of the external carotid artery and its branches.

During the angiographic study a progressive fall in the systolic blood pressure to 100 mm. Hg was observed. The pulse rate was 120 a minute, and there was still no spontaneous respiratory movement.

The patient died two hours after angiographic examination.

Autopsy disclosed a pronounced cerebellar pressure cone, together with a deep tentorial groove on the undersurface, mesially, of the two temporal lobes, and a deep notching on both sides of the midbrain, made by the free edge of the tentorium. The left lateral ventricle and the third and fourth ventricles were filled with clots. The hemorrhages originated in a softening in the left basal ganglia.

CASE 5.—*Frontal parasagittal meningioma in a man aged 74.*

The patient for five months had complained of constant headache, localized to the vertex and the neck. Loss of memory and vision supervened. For about a week before entrance to this hospital he had weakness of the lower limbs and disorders of speech. He became disoriented and confused.

Examination disclosed that he was disoriented and mildly euphoric, with speech disorders of the "executive" type. The fundi showed blurring of the optic disks and engorgement of the veins. The pulse rate varied from 50 to 60 a minute. The blood pressure at rest was 150 systolic and 100 diastolic. Within six hours an increase in systolic blood pressure to 220 mm. Hg developed; at the same time, the pulse rate was 48 a minute. At this stage angiograms were made, after percutaneous injection into the right common carotid artery. In the arteriograms the needle was seen to be inserted into the internal carotid artery for a distance of 1 in. The contrast medium was not observed to pass beyond the needle in the internal carotid artery. From the bifurcation of the internal carotid artery upward the opaque medium tapered away. On the other hand, the external carotid artery and its branches were extremely well filled, and a number of enlarged vessels were seen to supply the parasagittal growth.

One hour after angiographic examination the patient suddenly lost consciousness. Stiffness in the neck developed. Respiration became irregular, with increase in rate. The systolic blood pressure fell to 110 mm; the pulse rate was 44 a minute.

Operation was performed immediately, and a parasagittal meningioma, the size of a goose egg, chiefly on the right side but affecting both frontal lobes, was removed. The superior sagittal sinus was invaded and obliterated by the neoplasm.

After operation the patient recovered rapidly. There were no disorders of fundamental consciousness, although he was still confused. He did not display neurological signs of obliteration of the right internal carotid. The systolic blood pressure varied from 160 to 115 mm. and the diastolic, from 90 to 70 mm.

After transfer to his county hospital, he died, on the 24th postoperative day, of a pulmonary embolus.

Autopsy of the brain and the carotid arteries did not reveal vascular obliterations. Nor even the slightest sign of atheroma could be detected.

COMMENT

In the attempt to determine the cause of the holding up of the contrast medium in the internal carotid artery in these cases of a space-taking lesion, two types of impeded circulation must be considered, namely, the one due to lasting or transient obliteration of the artery, and the other unassociated with obliteration of the vascular lumen.

We propose, first, to consider the group of obliterative vascular lesions and then, after having found reason for rejecting them as the causal agent, to give attention to nonobliterative, or dynamic, changes in circulation, together with consideration of the specific physiopathological circumstances in which these angiographic disorders have been demonstrated.

Obviously, one set of vascular obliterations may be precluded as the causal agents, i. e., thrombosis and atheromatous and embolic occlusion of the internal carotid artery. No such abnormality was found at autopsy in any of the five cases. In Case 2 the possibility of such a condition was precluded even at an earlier stage, in that angiograms made when the patient's condition had improved showed a normal passage of the contrast medium through the cerebral arteries.

Although in the majority of the angiograms the block appeared rather abrupt, revealing the total diameter of the lumen, some of the films in Case 4 showed a gradual tapering off of the contrast medium in the internal carotid artery for a distance of about 3 in. (7.5 cm.). This is the configuration usually deemed characteristic of an atheromatous occlusion associated with secondary thrombosis.

The demonstration at autopsy of the absence of anatomical obliteration must increase the need of precaution when this diagnosis is to be made solely on the basis of the angiograms, at least when the condition is like that in the cases reported here. It would seem advisable to make a diagnosis of thrombosis or atheromatous occlusion of the internal carotid artery only in cases of an additional, complete or partial, collateral circulation from the opposite side.

The two remaining types of obliteration, namely, compression from the outside and spasm of the internal carotid artery, cannot, of course, be refuted as possible causes by referring to the demonstrated absence of anatomical obliteration of cerebral vessels at autopsy. These changes are transient. On the basis of the more immediate of these hypotheses, that of compression, it may be argued that in cases of increased intracranial pressure the internal carotid artery may be compressed against the base of the skull, where this vessel enters the cranial cavity. Even if, in certain circumstances, the intracranial pressure exceeds the pressure of some of the cerebral arteries, it would, as will be discussed later, seem unreasonable to assume a rise sufficient to compress the main trunk of the internal carotid artery. If such a rise in pressure developed, the basilar artery would for some time have been compressed against the base of the skull, since the side-pressure of this vessel is less than that of the internal carotid artery. A complete cessation of blood flow through the two internal carotid arteries and the basilar artery for more than a few minutes is inconsistent with the maintenance of life in man. In the present cases the disorders of circulation, as reflected in the angiograms, lasted for hours. Moreover, in no instance was the contrast medium found to be held up, exclusively or exactly, where the internal carotid artery enters the cranial cavity.

As for spasm, it would, in advance, seem unreasonable that a large artery, such as the internal carotid, would become completely obliterated, so that not even a faint amount of contrast medium could pass through. The improbability of this factor is further stressed by the fact that no spasm developed in the external carotid artery and its branches. On the contrary, these vessels were more densely filled than normal, and the caliber of the vessels was increased. This was so despite the exposure of the intimal coverings of the two vascular systems to the same irritant.

In some of the films changes were disclosed that must be taken to be inconsistent with the presence of an obliterative vascular process. Consecutive films taken after one and the same injection showed a slow passing cephalad of the contrast medium in the internal carotid artery.

Finally, it should be stressed that at the time that the angiograms were made the patient was in such a condition that the occurrence of an increased tendency to vasoconstriction would seem improbable, the more so since before the angiographic study papaverine had been administered to all.

In a consideration of the nonobliterative type of impediment to cerebral circulation, it may be well to discuss first some concepts of hemodynamics relevant to cerebral angiography. It should be said in advance that under normal conditions the hemodynamic factors are many and their interrelationship is complicated, and that in abnormal circumstances the problems may become even more complex.

In order that filling may be demonstrated at all in the angiogram, the rate of cerebral blood flow must be high enough to carry the contrast medium through the arteries within the period between the beginning of the injection into the common carotid artery and the time of exposure. If a marked diminution in rate of blood

flow occurs, an exposure made at the usual time after injection may result in films apparently showing a holding up of the medium—holding up that is independent of a reduction of the vascular lumen.

The rate of blood flow through the cerebral arteries must depend on the pressure in the internal carotid artery and the cardiac output; on the intracranial pressure; on the resistance in, that is, the degree of dilatation of, the cerebral vessels, and, finally, on the pressure in the jugular vein. An isolated rise in the jugular venous pressure will result in a rise in intracranial fluid pressure (Ryder and co-workers [1]). But this rise is only additive; consequently, it is of no importance to the situation we are considering, in which the intracranial pressure is high. If a sudden fall in intracranial pressure develops, the venous back pressure may come to play a part in the height of the intracranial pressure. Ryder and co-workers [2] also demonstrated the dependence of the intracranial pressure upon the cerebral volume flow. Changes in the volume flow through the brain may be evoked by changes in the cardiac output and in the arterial pressure. Thus, the last-named factors may influence mediately or immediately the intracranial pressure. This pressure is also influenced by the degree of dilatation of the cerebral vessels; that is, if the cardiac output remains unchanged, a dilatation will increase the volume of cerebral blood flow, resulting in a rise in intracranial pressure, whereas vascular constriction will be followed by the reversed condition. Despite a fall in arterial pressure in the internal carotid artery, elicited by amyl nitrite, the intracranial pressure will increase because of the dilatation of the cerebral vessels. On the contrary, a rise in arterial pressure of the internal carotid artery following the administration of arterenol will be associated with a decrease in intracranial pressure, due to cerebral vasoconstriction.

It is well established that the intracranial fluid pressure may be raised, in man and in monkeys, to considerable heights, that is, to heights surpassing those usually found in cases of an intracranial space-taking lesion, without any changes in the state of consciousness, muscular tone, or respiration and circulation. More than once we have observed increases, up to 1,400 mm. of water, or more, in patients with such lesions without these accompanying disorders. Evans and co-workers [3] have made several observations to the same effect, both in man and in experimental animals. If, however, the intracranial pressure equals the arterial pressure, a sudden increase in arterial pressure and in cardiac output is observed. Evans and co-workers [3] and Ryder and co-workers [1a] took the view that this increase in cardiac output and rise in arterial pressure are evoked reflexly. A detailed description of the reflex path was not given. The main factor in eliciting the reflex should be the interrelation of the arterial and the intracranial pressure, rather than the absolute height of intracranial pressure.

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1. (*a*) Ryder, H. W.; Espey, F. F.; Kristoff, F. V., and Evans, J. P.: Symposium on Intracranial Vascular Abnormalities: Observations on the Interrelationships of Intracranial Pressure and Cerebral Blood Flow, J. Neurosurg. **8**:46, 1951. (*b*) Ryder, H. W., and others: Effect of Changes in Systemic Venous Pressure on Cerebrospinal Fluid Pressure, A. M. A. Arch. Neurol. & Psychiat. **68**:175, 1952.

2. Ryder, Espey, Kristoff, and Evans.[1a] Ryder, H. W., and others: Influence of Changes in Cerebral Blood Flow on the Cerebrospinal Fluid Pressure, A. M. A. Arch. Neurol & Psychiat. **68**:165, 1952.

3. Evans, J. P., and others: Experimental and Clinical Observations on Rising Intracranial Pressure, A. M. A. Arch. Surg. **63**:107, 1951.

So far as we are aware, the majority of these observations have been made in cases in which no obliteration of the passage of ventricular fluid had developed. A rise in cerebrospinal fluid pressure, affecting equally the supratentorial space and the subtentorial and spinal spaces, is not, of course, followed by displacement of the brain; consequently, no herniation of the brain stem into the tentorial incisure develops. Under such circumstances the explanation advanced for the evocation of the reflex increase in arterial pressure seems reasonable, though details are unknown.

It should be recalled, however, that the five cases reported here were all cases of a localized space-taking lesion, whether it was a neoplasm or an intracerebral hemorrhage with clotting. In two instances the lesion led to an immediate obliteration of the passage of the ventricular fluid; this may, other things being equal, result in a rise in the supratentorial pressure, followed by secondary herniation of the brain stem into the tentorial incisure. In the remaining cases the displacement, by the supratentorial expanding lesion, of parts of the temporal lobe and of the brain stem into the incisure was the initial process. This may lead to secondary obliteration of the cerebral aqueduct. In fact, tentorial pressure cones, with notching of the brain stem, and cerebellar pressure cones, in some instances associated with anatomical obliteration of the cerebral fluid passage, were disclosed in all but one case. In this case (Case 5) the patient died of pulmonary embolism 24 days after removal of the primary space-taking lesion; sufficient time, therefore, had lapsed for signs of herniation to disappear. All patients displayed signs that are usually taken as an indication of severe involvement of the brain stem, such as loss of consciousness (coma) associated with severe respiratory and circulatory disorders and with changes in muscular tone, in the nature of decerebrate rigidity. It is worth noting that in the present two cases of intracerebral hemorrhage the hemorrhagic lesion acted like a suddenly developed, expanding supratentorial lesion, leading to severe herniation into the incisure. This is the more interesting in that in one of the cases on the basis of which the interrelation of increased intracranial pressure and arterial pressure was originally discussed an intracerebral hemorrhage occurred (Cushing [4]). In our opinion, it is far from rare that hemorrhage into the cerebral hemisphere leads to severe transtentorial herniation of the brain stem.[5]

Some of the experimental observations on record may be immediately relevant to the question of herniation of the brain stem. Ryder and co-workers [1a] found that continued injection of oil into the hemisphere finally resulted, in monkeys, in irregular deep respiration, progressing to apnea, and in a sudden and more lasting increase in arterial pressure and a concomitant rise in intracranial pressure, due to an increase in volume of cerebral blood flow. These authors considered the rate of cerebral blood flow more important than the volume of the space-taking lesion in maintaining the raised intracranial pressure. Eventually, in the dying animal, they observed cardiac dysrhythmia, together with changes in the ventricular complexes in the electrocardiogram. This was followed by a fall in arterial pressure and in cardiac output, invariably associated with a fall in the intracranial pressure. In such circumstances the fall in intracranial pressure occurs regardless of the

4. Cushing, H.: The Blood Pressure Reaction of Acute Cerebral Compression, Illustrated by Cases of Intracranial Hemorrhage, Am. J. M. Sc. **125**:1017, 1903.

5. Unpublished data.

size of the space-taking lesion, so that at the time when the activity of the heart ceases, the intracranial pressure is zero. The initial "reflex" increase in arterial pressure is taken to be far more powerful, in certain circumstances, than is the control by anoxia and increase in carbon dioxide tension of the intracranial pressure and rate of cerebral blood flow.

Although, in these experimental space-taking lesions, after continued injection of small amounts of oil into the hemisphere, conditions may eventually be brought about for cerebral displacement and secondary involvement of the brain stem at the level of the mesencephalon, one cannot, in reality, tell whether this is so. No mention has been made by Ryder and associates of pathoanatomical changes in the brain. After a similar procedure, however, that is, injection of paraffin into the white matter of the hemisphere in cats, Perret [6] and Sorgo [7] described a marked displacement of mesial parts of the temporal lobe into the tentorial incisure, obliterating the cisterns surrounding the brain stem. In the latter structure deep notching, made by the free edge of the tentorium, was found. These animals displayed changes in respiration, circulation, and muscular tone similar to those described above.

The common occurrence, in cases of space-occupying intracranial lesions, of herniation of the midbrain, usually together with the two hippocampal gyri, into the incisure is well known.[8] Its relation to a rise in supratentorial pressure has been mentioned above. Changes in circulation, transient or lasting, may ensue, such, first, as ischemia, and, later, impediment of venous outflow and edema (Moore and Stern [9]; Scheinker [10]). These changes need not be confined to the midbrain. The diencephalon and the pons may become involved. So far, we cannot tell exactly how this involvement of the brain stem may influence circulation in the brain and in the remaining parts of the organism. The possibility, however, cannot be ignored that a certain degree of neuronal dysfunction, elicited by circulatory changes, in some parts of the brain stem is followed by an arterial pressor response, and that severer neuronal dysfunction and abolition of function, developed on the same ground, are followed by a fall in blood pressure and a decrease in cardiac output, progressing to cessation of the activity of the heart.

Viewed from this angle, conditions may develop that may be mediately or immediately related to the processes under consideration. Even though the rise in supratentorial fluid pressure is not excessive, the involvement of the brain stem may result "reflexly" in a primary rise in arterial pressure. Because of the blocking of the passage of the ventricular fluid, the pressure in the supratentorial space will

6. Perret, G. E.: Experimentelle Untersuchungen über Massenverschiebungen und Formveränderungen des Gehirns bei raumbeengenden Prozessen, Zentralbl. Neurochir. **5**:5, 1940.

7. Sorgo, W.: Experimentelle Untersuchungen über die Klinik der Verquellung der Cysterna ambiens, Deutsche Ztschr. Nervenh. **149**:271, 1939.

8. Schwarz, G. A., and Rosner, A. A.: Displacement and Herniation of the Hippocampal Gyrus Through the Incisura Tentorii: A Clinicopathologic Study, Arch. Neurol. & Psychiat. **46**:297, 1941.

9. Moore, M. T., and Stern, K.: Vascular Lesions in the Brain-Stem and Occipital Lobe Occurring in Association with Brain Tumours, Brain **61**:70, 1938.

10. Scheinker, I. M.: Transtentorial Herniation of the Brain-Stem: A Characteristic Clinicopathologic Syndrome; Pathogenesis of Hemorrhages in the Brain-Stem, Arch. Neurol. & Psychiat. **53**:289, 1945; Cerebral Swelling: Histopathology, Classification and Clinical Significance of Brain Edema, J. Neurosurg. **4**:255, 1947.

remain higher than the subtentorial one. This will favor a further herniation of the brain stem and, eventually, a severer neuronal dysfunction in these structures. The final outcome of this process will be failure of the activity of the heart. If the involvement of the brain stem is extremely sudden and severe, the circulatory response may be depressor in type. A fall in cardiac output at this stage may for a brief period be associated with a rise in the venous "back pressure," increasing further the intracranial pressure, so that the condition for a satisfactory circulation through the brain becomes even worse.

In the light of these considerations, the series of events in the present cases may briefly be reviewed.

Artificial respiration with pure oxygen was administered in all cases. A closed system with a "to-and-fro" absorber was used. Consequently, the possibility of interference with cerebral circulation based on changes in carbon dioxide tension can be precluded.

Since we have no immediate measurement of the cardiac output, the interrelations of intracranial pressure and blood pressure will be considered exclusively. If the blood flows into the brain at all, it is clear that the arterial pressure of the internal carotid must be higher than that of the cerebral vessels. The relevant pressure, in this connection, is the diastolic, rather than the systolic.

The initial supratentorial fluid pressure in Case 2 was 180 mm. of water. After insufflation of air into the lateral ventricles a sudden rise, to a minimum of 1,140 mm. of water, developed. Just before that time the diastolic blood pressure was measured as 80 mm. Hg, or 1,088 mm. of water, that is, below the pressure of the supratentorial fluid. This calculation, naturally, cannot be taken literally. The arterial pressure mentioned above is not that of the internal carotid, but that of the brachial, artery, the pressure in the latter being considerably lower than in the former; moreover, the two measurements were not made at exactly the same time. But the fall in arterial pressure may result in such an interrelation of intracranial and arterial pressures that, with unchanged cardiac output, a notable diminution in rate of cerebral blood flow occurs. This may readily explain the angiographic results.

In Case 1 the spinal fluid pressure was 100 mm. of water. This may not, however, in cases of tentorial herniation, be taken to indicate the height of the supratentorial fluid pressure. In this case, and in Case 3, a fall in systolic blood pressure (brachial artery) to 70 mm. Hg had occurred during the angiographic study. The diastolic pressure may be assumed to be about 20 mm. Hg lower, that is, 650 mm. of water. A pressure in the supratentorial fluid of that height is by no means improbable. This probable decrease in pressure differences may lead to a diminution of cerebral blood flow.

The pronounced fall in Case 4 in fluid and blood pressures and the occurrence of apnea indicate a severe lesion of the brain stem, resulting in a fall in cardiac output and diminished blood flow through the brain, and, eventually, in the death of the patient, two hours later. In this case, also, the fall in rate of cerebral blood flow is the most probable factor in the explanation of the holding up of the contrast medium in the internal carotid artery.

In Case 5 a marked rise in the systolic blood pressure, from 150 to 200 mm. Hg, developed before angiograms were made. This increase was associated with a fall in pulse rate from 60 to 48 a minute. Immediately after angiography, the

systolic blood pressure was 110 mm. Hg, and the pulse rate was 44 a minute. One hour later, the patient suddenly became unconscious, stiffness of the neck developed, and respiration became embarrassed. In this case the changes in the arteriograms may reasonably be taken to indicate a notable diminution of blood flow through the internal carotid artery, together with a marked increase in blood flow through the tumor-feeding external carotid artery and its branches.

It is safe, we think, to conclude that a holding up of the contrast medium seen in angiograms made when signs of severe herniation of the brain stem into the tentorial incisure are present cannot be taken, out of hand, to indicate an anatomical or a functional obliteration of the vessel. In some instances, the block may be due to a diminution of cerebral blood flow, evoked mediately by the herniation of the brain stem.

SUMMARY

Five cases of an intracranial space-taking lesion are described, in all of which a holding up of the contrast medium in the internal carotid artery appeared in the angiograms. Blocking of the passage of ventricular fluid and herniation of the brain stem into the tentorial incisure were disclosed in all cases.

The cause of the holding up of the medium in these cases is discussed. The block cannot be taken to indicate, out of hand, obliteration either anatomically or by compression and spasm of the intracranial arteries. In fact, autopsy did not reveal anatomical obliteration in any case.

The view is taken that they result from a notable diminution of cerebral blood flow, ensuing mediately upon involvement of the brain stem.

News and Comment

CARBON DIOXIDE RESEARCH ASSOCIATION, INC.

Carbon Dioxide Research Association, Inc., was incorporated under the laws of the state of New York on June 26, 1953. This association succeeds the Committee on Carbon Dioxide Research. The officers of the Association are as follows:

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INTERNATIONAL CONGRESS OF ELECTROENCEPHALOGRAPHY AND CLINICAL NEUROPHYSIOLOGY

The International Congress of Electroencephalography and Clinical Neurophysiology will be held at the Agassiz House, Cambridge, Mass., Aug. 16-22, 1953. Dr. Robert S. Schwab, Massachusetts General Hospital, Boston 14, is the secretary-general.

THE AMERICAN PSYCHOSOMATIC SOCIETY

The American Psychosomatic Society will hold its eleventh annual meeting at the Jung Hotel in New Orleans on Saturday and Sunday, March 27 and 28, 1954.

The program committee would like to receive titles and abstracts of papers for consideration for the program by Dec. 1, 1953. The time allotted to the reading of each paper will be 15 to 25 minutes. The committee is interested in investigations in the theory and practice of psychosomatic medicine as applied to adults and children in all the medical specialties, and in contributions in psychophysiology and ecology.

The program committee requests that abstracts be submitted in quadruplicate to the chairman, Dr. George L. Engel, 551 Madison Ave., New York 22.

INSTITUTE OF PSYCHIATRIC TREATMENT

A three-day institute of psychiatric treatment will be held at the Boston State Hospital, Boston, Oct. 1-3, 1953, under the direction of Dr. Leo Alexander and Dr. Robert Arnot. The topics to be considered will include treatment of psychoneuroses and borderline states, treatment of manic-depressive illness, and treatment of schizophrenia. Applications for admission may be made to Dr. Leo Alexander, 433 Marlboro St., Boston.

APPOINTMENT OF DR. ROBERT WARTENBERG

Dr. Robert Wartenberg, of San Francisco, has been appointed *Honorarprofessor* (Titular Professor) of the University of Freiburg i. Br., Germany.

Books

La désorganisation de la personnalité. By Henri Baruk. Price, 5 fr. 6. Pp. 161. Presses universitaires de France, 108 Boulevard Saint-Germaine, Paris, 1952.

This brief but logical and thought-provoking book is written by the chief physician of the famous Maison National de Charenton. The author is an experienced psychiatrist who grew up with the problem of mental illness, since his father was also a psychiatrist. The book is divided into two parts, of which the first deals with disorganization of the personality due to natural causes and the second with disorganization provoked by the physician for therapeutic purposes.

The author insists, first, on the importance of the sentiment of personality for the well-being of the individual and of society and studies the causes of a sentiment of depersonalization. There are many hypotheses, mostly purely verbal descriptions or assumptions based on vague physiological data concerning vascular, hormonal, or endocrine perturbations. The last seem to be at the bottom of our sentiment of the existence and life of our body. But the sentiment of the proper functioning of our psychic life seems to be even more important. The author studies the various abnormal sentiments of influence, of escape of thought, of automatism, of vacuum which indicate how precious to the human being is his own personality, with all its weaknesses and sufferings; he needs to believe that he acts in accord with his own volition. The author has done a great deal of work with the production of cataleptic and catatonic phenomena by means of drugs which "poison" volition. He describes these phenomena and discusses their relation to Janet's conception of psychological tension and its fluctuations. He insists on the curability of these disintegrations produced by toxic causes, since the personality is usually not destroyed in such cases.

In the second part, the author studies the methods of artificial disintegration in vogue, which he calls methods of a sorcerer's apprentice. He recounts the long history of narcoanalysis in France, beginning with the famous treatise of Moreau de Tours in 1845, and describes his own experiences, ending with the statement that the method is of very limited usefulness and brings cures only of hysterical phenomena. He also laments the use of shock therapy, which, when successful, brings in its wake permanent alterations of the personality, but he is especially opposed to lobotomies, which produce permanent alterations of social and moral adjustment and are followed by epilepsy or worse. He insists on the difficulty of establishing a prognosis in mental cases and notes that at the Charenton 88% of the patients get well within two years of onset without such drastic treatment and another 12% later, even as long as 16 years after the onset. He believes that it is not morally justifiable to mutilate the brain for the purpose of making the care of the patient easier. He doubts whether it is justifiable to produce a grave alteration of the personality in order to get rid of certain inconvenient symptoms. He notes how easily such therapeutic experimentation can degenerate into simple experimentation and protests against calling these operations biological treatments.

This thoughtful little book should be read and pondered by every psychiatrist.

Diseases of Muscle: A Study in Pathology. By Raymond D. Adams, D. Denny-Brown, and Carl M. Pearson. Price, $16. Pp. 556, with 347 illustrations. Paul B. Hoeber, Inc., (Medical Book Department of Harper & Brothers), 49 E. 33d St., New York 16, 1953.

Adams, Denny-Brown, and Pearson are to be congratulated on bringing together in this book a great body of facts which up to this time have been scattered throughout special journals on pathology, physiology, neurology, and chemistry. A book on the striated muscle has long been needed; after all, over half of one's body mass is muscle, and in most courses on pathology not one-hundredth of the assigned hours is devoted to the pathology of muscle. Here is a scholarly, detailed, and meticulously documented monograph on the embryology, histology, tissue pathology, and pathological reactions of skeletal muscle. It is well written and beautifully illustrated with photomicrographs, drawings, and myographs. The difficult problem of classification of the diseases of muscle is solved by basing the classification on etiology, in the few cases

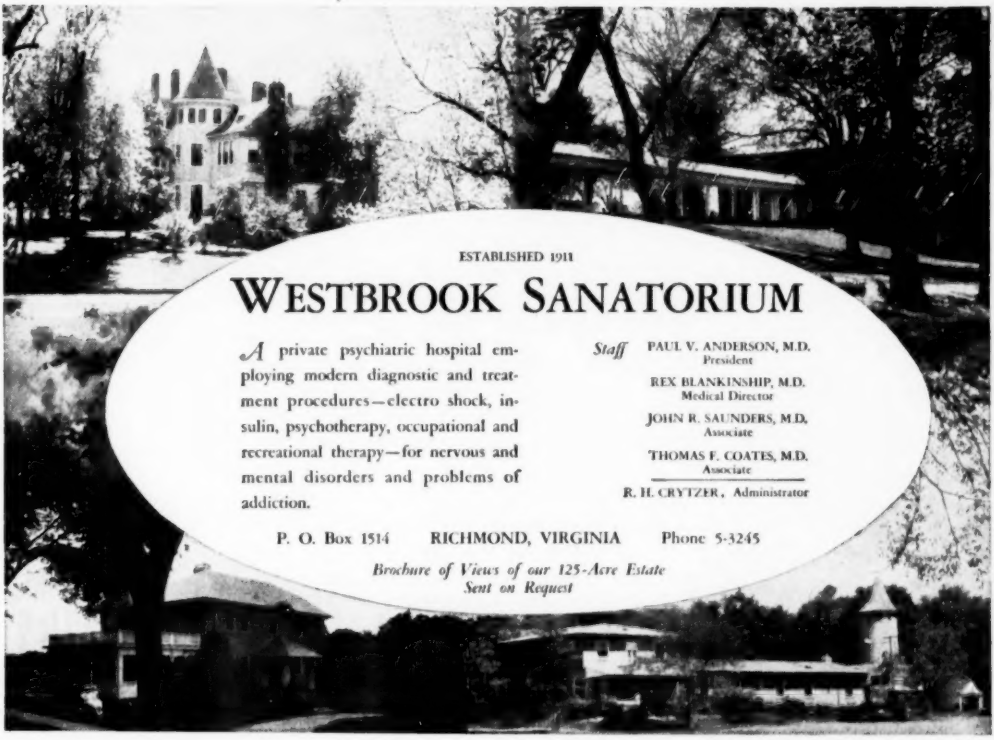
in which it is known, and otherwise basing it on histopathology. The authors considered the possibility of describing the diseases in physiological groups, but probably wisely decided to stick largely to morbid anatomy. They remark: "Further consideration, however, makes it clear that such a plan, though attractive, is premature, and gives a misleading impression of finality. Close inspection of the relevant data concerning each of these diseases discloses the extremely hypothetical nature of such grouping, and of its basis in current schemes of fundamental physiology. The chief purpose of this review will have been well served if it stimulates and leads to a further investigation toward a more complete definition of muscular activity and its disorders." Nevertheless, after reading the section on muscular dystrophies, endocrinopathies, chemistry, and neural atrophies, one is tempted to generalize to the extent of thinking of the dystrophies as hereditary disorders of the endocrine glands and muscular metabolism, while the neural atrophies seem to belong to a large group of heredodegenerative diseases of neurones —from retina to ventral horn cell. The old discussion about the differentiation of amyotonia congenita (Oppenheim's disease) from infantile progressive muscular atrophy (Hoffmann-Werdnig syndrome) is disposed of by practically eliminating the former as a recognizable clinical entity and describing the latter as a degenerative disease of the ventral horn cells.

Part 1 of this carefully planned volume deals with embryology, histology, and blood supply, in 83 pages. Part 2 is perhaps the most enlightening to the general physician by its discussions of experimental pathology and general reactions of muscle to disease. Here are discussed denervation atrophy, disuse atrophy, regeneration of muscle, contracture, rigor, and fibrillary contraction. A whole field of physiology and pathology is reviewed in about 100 pages, and Denny-Brown's own researches in this area are integrated with the others, giving an authoritative and modern tone to the whole exposition. Especially important for neurologists and orthopedic surgeons are the discussions of degeneration and regeneration and of abnormal contractions, such as contracture and fibrillation. The latter is described as due to the minute traces of acetylcholine normally found in the body fluids acting on the hyperexcitable muscle during its atrophy. The reactions of muscle to injury, infection, toxin, and vitamin deficiency are also of great practical importance.

For one who would like to see a specific histological picture for each disease of muscle, Part 3, on special pathology, will be a little disappointing, because the reactions are rather more general than specific. The muscular dystrophies differ from each other more in anatomical distribution than in histological picture. Myotonia and myotonic dystrophy are probably alike in chemical pathology but differ in genotype. The description of the many rare inflammations and tumors of muscle make interesting reading. The chapter on traumatic and circulatory diseases clears up many misunderstandings. It will be of value to athletic trainers in the understanding of such common conditions as stiff muscles and "shin splints." Trauma and vascular occlusions are the important causes and are often combined.

The extensive knowledge brought together in this book is important to all physicians, especially those in the fields of pathology, neurology, and orthopedics. For the general practitioner some of the commonest and most annoying of human ills still remain unexplained: the fatigues, stiffnesses, cramps, and aches of skeletal muscle.

This distinguished book fills a long-felt need.



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